Use of a computer-assisted registration program to investigate antibiotic prescription and antibiotic resistance in the intensive care unit

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Onderzoek van het antibioticumvoorschrift en de antibioticumresistentie in de dienst intensieve zorg met behulp van een elektronisch geassisteerde registratie

Liesbet De Bus

Thesis submitted in fulfillment of the requirements for the degree of Doctor in Medical Sciences

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Aan mijn ouders, die kansen creëerden, en nu nog steeds

Aan Ruben, Daan, Arthur en Christophe

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SCIENTIFIC SUMMARY

Antibiotic stewardship was recently defined as "a coherent set of actions which promote using antimicrobials responsibly" in an era of increasing antibiotic resistance and few antibiotics in the development pipeline.[1] The intensive care unit (ICU) is a key consumer of antibiotics in the hospital. As the antibiotic decision-making process is complicated by diagnostic uncertainty and potential involvement of multidrug-resistant (MDR) pathogens, the ICU constitutes an important target for antibiotic stewardship programs (ASP).

Detailed monitoring of antibiotic prescription, infection diagnosis and antibiotic resistance patterns is essential to identify meaningful stewardship intervention targets and to assess the impact of a stewardship action following its implementation. Computerization of the patient ICU record and introduction of computerized physician order entry (CPOE) created new possibilities to support this surveillance process. A software program with the acronym COSARA: 'Computer-based Surveillance and Alerting of nosocomial infections, Antimicrobial Resistance and Antibiotic consumption in the ICU' was developed by a consortium of the Ghent University Hospital ICU department and the Department of Information Technology of the Faculty of Engineering of Ghent University. COSARA serves as a data visualization dashboard on infection management for the individual ICU patient and has been available on every personal computer dedicated to patient care since 2010. As such, COSARA facilitates linking of antimicrobial prescription data, microbiology data and clinical information of each individual ICU patient during the daily workflow of the ICU physician, which results in the building up of a large longitudinal relational database on infection.

In a first stage of this PhD project we evaluated the validity of COSARA as a surveillance tool and assessed the practical feasibility of continued infection registration. Surveillance through COSARA was compared with paper-based surveillance (PBS) based on Centers for Disease Control and Prevention (CDC) criteria for three infection types: bloodstream infections, respiratory tract infections and urinary tract infections. Good agreement between both surveillance methods was recorded. In addition, surveillance through COSARA required less than one-third of the time spent on PBS.

In a second stage of this research project we aimed to acquire more insight in our local antibiotic prescription practices and microbiological resistance patterns based on in-depth analyses of the datasets that were constructed through the use of COSARA.

On the one hand, we performed a descriptive analysis of a dataset covering four years of surveillance to get a bird's eye view of local antibiotic prescribing practices. This evaluation

revealed that the antibiotic burden is high in our ICU. However, only half of the overall antibiotic consumption is used to treat infections that were classified as highly probable. As such, we were able to identify meaningful areas for improvement of our prescribing patterns.

On the other hand, we evaluated the potential impact of 3 highly recommended ASP interventions in our ICU. Firstly, we assessed the potential of a treatment guideline for empirical antibiotic prescription in hospital-acquired pneumonia (HAP) based on local ecology data and the added value of incorporating surveillance culture (SC) results in such an algorithm. We found no difference in appropriate antibiotic coverage rates between the antibiotic treatment that was actually prescribed by physicians in our ICU and the treatment proposed by the algorithms. Addition of SC results in the guidelines, however, resulted in a significant reduction of the use of broad-spectrum agents.

Secondly, we analyzed the frequency and determinants of de-escalation (i.e. reduction of the antibiotic spectrum) of empirical anti-pseudomonal beta-lactam antibiotics and its effect on patient outcome. Our results showed that de-escalation was performed in one-quarter of the prescriptions. In multivariate analysis, de-escalation was solely associated with the identification of etiologic pathogens. Surprisingly, the duration of the antibiotic course in the ICU was significantly longer in the de-escalated prescriptions compared to prescriptions that were not altered during the treatment course. In addition, the emergence of antibiotic-resistant bacteria after exposure to anti-pseudomonal beta-lactam antibiotics was not lower following de-escalation.

Thirdly, we calculated the potential saving in antibiotic consumption for three antibiotic classes (glycopeptides, oxazolidinones and carbapenems), by a systematic assessment of the ongoing need of an antibiotic treatment 48-72 h following its initiation. One third of carbapenem consumption was classified as potentially unjustified by previously defined criteria, compared to only 13% of glycopeptide/oxazolidinone use.

In conclusion, by using COSARA, we were able to construct a dynamic longitudinal dataset on infection in our ICU. Over the last few years, we acquired detailed insight in local antibiotic prescription practices and antibiotic resistance patterns, which is of inestimable value in the further expansion of an ASP. Continuous merging of antimicrobial prescription data, microbiology data and clinical information of each ICU patient, represents the strength our surveillance strategy. COSARA enables integration of this process in the daily workflow of the ICU physician and as such, allows for sustained prospective surveillance. However, we have to acknowledge that the persistent commitment of dedicated physicians remains vital for its chances of success.

WETENSCHAPPELIJKE SAMENVATTING

De resistentie van bacteriën voor antibiotica is de laatste decennia aanzienlijk toegenomen. De ontwikkeling van nieuwe antibiotica is evenwel gestagneerd en dwingt gezondheidswerkers tot verdere acties. 'Antibiotic stewardship' wordt gedefinieerd als "een samenhangend geheel van interventies die als doel hebben het verantwoord gebruik van antimicrobiële middelen te bevorderen".[1] De dienst Intensieve Zorg (IZ) is verantwoordelijk voor een aanzienlijk aandeel in het antibioticumverbruik in het ziekenhuis. De complexe diagnostiek in deze patiëntenpopulatie en de mogelijke betrokkenheid van multidrug-resistente (MDR) kiemen bemoeilijkt de beslissing rond het al dan niet starten van antibiotica bij kritiek zieke patiënten en de correcte keuze hierbij. IZ-afdelingen vormen dan ook een belangrijke doelgroep voor 'Antibiotic stewardship'-programma's (ASP).

Een continue en gedetailleerde monitoring van het antibioticumvoorschrift, de infecties en de antibioticumresistentie kan de identificatie van potentiële interventies en de evaluatie van de impact hiervan na implementatie bevorderen. De invoering van het elektronisch patiëntendossier en het elektronisch medicatievoorschrift op IZ heeft dit documentatieproces duidelijk beïnvloed over de voorbije jaren. De dienst IZ van het Universitair Ziekenhuis Gent ontwikkelde in samenwerking met de vakgroep Informatietechnologie van de faculteit Ingenieurs-wetenschappen van de Universiteit Gent een elektronisch registratieprogramma met de naam COSARA: 'Computer-based Surveillance and Alerting of nosocomial infections, Antimicrobial Resistance and Antibiotic consumption in the ICU'. Deze software integreert alle infectie-gerelateerde informatie en presenteert deze aan de gebruiker onder de vorm van een continue, visuele samenvatting en is sinds 2010 beschikbaar op iedere IZ computer. COSARA faciliteert het maken van connecties tussen antibioticumdata, microbiologiegegevens en klinische informatie van een individuele IZ patiënt en laat toe dat dit proces geïntegreerd wordt in de dagelijkse klinische zorg van de IZ arts. Deze gecombineerde gegevens worden opgeslagen in een gedetailleerde, longitudinale database.

In het eerste deel van deze thesis evalueerden we de validiteit van COSARA als monitoring systeem en gingen we na in hoeverre deze registratiemethode haalbaar was over langere tijdsperiodes. Voor drie geselecteerde infectietypes (bloedstroominfecties, luchtweginfecties en urineweginfecties) werd een vergelijking gemaakt tussen de documentatie met behulp van COSARA en de 'klassieke' monitoring, waarbij een zorgverstrekker schriftelijk de infecties registreert op basis van de Centers for Disease Control and Prevention (CDC) criteria. We vonden een goede overeenstemming tussen beide strategieën. Registratie met behulp van

COSARA nam echter slechts een derde van de tijd die nodig was voor de 'klassieke' registratie in beslag.

Het tweede deel van ons onderzoek was gericht op het verkrijgen van meer inzicht in ons lokaal antibioticumvoorschriftgedrag en onze lokale antibioticumresistentiepatronen, gebaseerd op diepgaande analyses van de datasets die werden opgebouwd met behulp van COSARA.

Enerzijds wilden we een globaal overzicht verkrijgen van ons antibioticumgebruik op basis van een beschrijvende analyse van een dataset die de gecollecteerde gegevens bevat van alle IZ patiënten over een periode van 4 jaar. Deze evaluatie toonde aan dat het antibioticumverbruik hoog is in onze IZ en dat slechts de helft van het totale verbruik aangewend wordt voor de behandeling van infecties met een hoge graad van zekerheid. Dit liet ons toe om deelgebieden te identificeren die in aanmerking komen voor ASP interventies.

Anderzijds analyseerden we de potentiële impact in onze IZ van drie sterk aanbevolen ASP interventies. Als eerste evalueerden we de meerwaarde van een richtlijn, ontwikkeld op basis van lokale antibioticumresistentiecijfers, voor de empirische behandeling van een pneumonie ontstaan in het ziekenhuis. Daarnaast gingen we de toegevoegde waarde na van het incorporeren van de resultaten van routine surveillantie culturen (SC) in een dergelijk algoritme. Er werd geen verschil genoteerd in de adequaatheid van de antibiotische behandeling die in realiteit toegediend werd aan de patiënt en deze die aangeraden werd door de bovenstaande richtlijnen. Het inbouwen van de resultaten van de SC resulteerde echter wel in een significante reductie in het gebruik van breedspectrumantibiotica.

Een tweede analyse was gericht op antibiotische deëscalatie, een stewardship-strategie die zich toespitst op het vernauwen van het antibiotisch spectrum. We gingen na hoe vaak een empirisch beta-lactam antibioticumvoorschrift met activiteit voor *Pseudomonas* gedeëscaleerd werd in onze IZ, wat de determinanten voor deëscalatie waren en wat de impact hiervan was op de evolutie van onze patiënten. Onze resultaten toonden aan dat deëscalatie werd uitgevoerd in een vierde van de voorgeschreven behandelingen en dat dit in multivariaat analyse enkel geassocieerd was met de identificatie van de ziekteverwekkende kiem. Een opmerkelijke bevinding was dat de duur van de antibioticumkuur op IZ significant langer was indien werd gedeëscaleerd. Deëscalatie ging niet gepaard met een afname van het aantal verworven resistente kiemen.

Ten derde, trachtten we te berekenen in welke mate we het verbruik van drie antibioticumklassen (glycopeptiden, oxazolidinone en carbapenems) zouden kunnen beperken door op systematische wijze na te gaan of deze therapie nog steeds aangewezen is 48 tot 72 uur na de start van een behandeling. We konden concluderen dat volgens een set van eerder

gedefinieerde criteria, 33% van het carbapenem-verbruik potentieel ongerechtvaardigd was in vergelijking met amper 13% van het glycopeptiden/oxazolidinone-verbruik.

We kunnen besluiten dat het gebruik van COSARA ons in staat heeft gesteld een dynamische en longitudinale dataset op te bouwen rond infecties op IZ. Over het verloop van de voorbije jaren hebben we meer inzicht verkregen in ons lokaal antibioticumvoorschriftgedrag en onze lokale antibioticumresistentie, wat van onschatbare waarde is in de uitbouw van een ASP. Het basisprincipe en de sterkte van onze monitoringsstrategie bestaat uit het longitudinaal combineren van antibioticumdata, microbiologiegegevens en klinische informatie voor iedere IZ patiënt. Met behulp van COSARA is het mogelijk om dit proces te integreren in de dagelijkse klinische praktijk van de IZ arts, waardoor deze registratie kan aangehouden worden over langere tijdsperiodes. Een continue inzet en toewijding van de IZ arts blijft echter cruciaal.

“Information is the lifeblood of medicine and health information technology is destined to be the circulatory system for that information.”

David Blumenthal

1 INTRODUCTION

A. INFECTION AND ANTIBIOTICS IN CRITICAL ILLNESS

Critical illness caused by infection, either acquired in the community or associated with healthcare settings, is one of the most common reasons for intensive care unit (ICU) admission.[2] In addition, ICU patients are prone to develop new infections for multiple reasons: e.g. the presence of invasive catheters, the need for invasive ventilation, a post-operative, weakened and/or immunosuppressed status.[3-5] A large multicenter point prevalence study collecting data in 75 different countries showed that an infection was present in 51% of the patients admitted to the ICU and that 71% of the patients received an antibiotic treatment on the day of study.[2] Smaller-scale studies performed over longer periods of time reported comparably high rates of infection and antibiotic use, although these figures varied between different types of ICUs and subsets of patients.[6-9]

The outcome of an infected patient is positively affected by the administration of adequate antibiotic therapy covering all causative pathogens early in the course of the infection.[10-13] In the case of the ICU patient, this can be quite challenging. First of all, multiple non-infectious conditions frequently occurring in ICU patients can mimic an infection in its early stage and complicate the diagnostic process. Some examples are: fever in the patient with an intracerebral bleeding, elevated C-reactive protein (CRP) indicating inflammation in the absence of infection in case of acute pancreatitis, the development of an acute respiratory distress syndrome (ARDS) secondary to trauma or inhalation and hemodynamic instability resulting from post-operative bleeding. In addition, the selection of an appropriate empirical[1] treatment strategy is hampered by increasing antimicrobial resistance rates.[14, 15] This is especially the case for the present-day, complex ICU patient with underlying chronic illness or protracted hospitalization stay. Prior antibiotic use, hospital readmission and acute renal replacement therapy are only some of the factors that are considered to be a risk for the involvement of multidrug-resistant (MDR) pathogens.[16-18] The aforementioned difficulties have enforced the authors of the 'Surviving Sepsis Campaign' (SSC) guidelines, which are international instructions for the management of sepsis and septic shock, to advocate timely administration of broad-spectrum, often combination, antibiotic therapy to cover all likely pathogens. It is recommended to tailor the empirical antibiotic scheme to the individual patient's comorbidities, prior known colonization status and antibiotic courses, current clinical status and to local epidemiology.[18] As soon as

[1] Empirical antibiotic treatment is defined as a treatment initiated in the absence of microbiological pathogen identification and susceptibility results.

microbiology results are available and/or the clinical course of the patient becomes clear, physicians are encouraged to narrow the spectrum of this empirical treatment whenever possible.

In summary, making adequate antibiotic treatment decisions for the critically ill patient is not straightforward. Detailed, timely and easy accessible patient and infection related information is required to guide the ICU physician in his/her antibiotic decision-making process.

B. ANTIBIOTIC STEWARDSHIP AND THE ICU

Since the discovery of the first antibiotic agent, benzylpenicillin in 1928 by Sir Alexander Fleming, antibiotics have proven to be live-saving and indispensable in an ICU environment.[19] Unfortunately, the liberal deployment of antibiotics was closely followed by the emergence of resistant bacterial strains.[20] Once very potent antibiotic agents are no longer considered to be a safe empirical treatment option, due to concerns about the possible involvement of MDR pathogens. At the present time, it is a well-known fact that antibiotic exposure promotes the emergence of antibiotic resistance.[21-24] Bearing this in mind, it is quite troublesome to realize that 30 to 60% of antibiotic prescriptions in the ICU are superfluous or inappropriate.[23]

In 1996, McGowan and Gerding made a plea for the optimization of antibiotic consumption to refrain the growing problem of antibiotic resistance. In their statement the term 'antimicrobial stewardship' was introduced.[25] Over the past 20 years this concept has been refined. In a consensus statement from the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS), antimicrobial stewardship is currently defined as "coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic drug regimen including dosing, duration of therapy and route of administration".[26] The ultimate goal of these interventions is finding the right balance between: a) ensuring a good clinical outcome for the present patient and b) minimizing adverse effects related to antibiotic use i.e. antibiotic toxicity, selection of MDR and increasing costs for the present as well as the future patient and society.[27] The need for a well-designed antimicrobial stewardship program (ASP) is increasingly being recognized and has even been incorporated in the National Action Plan for Combating Antibiotic-Resistant Bacteria published by the White House in 2015.[28]

Guidelines for the implementation of these ASP in hospital settings are issued and updated regularly.[29] It has been stressed that the selection of stewardship actions must be carried out in a judicious manner to ensure maximum efficiency of actions in the current setting of limited healthcare personnel and financial resources. Figure 1 displays the crucial steps in the implementation process of a stewardship intervention.

Over the last few years, a growing body of evidence demonstrating the positive effects of ASP became available.[30-32] Unfortunately, large-scale studies performed over longer periods in time are scarce and issues about sustainability and generalizability of these effects cannot be answered based on the available data.

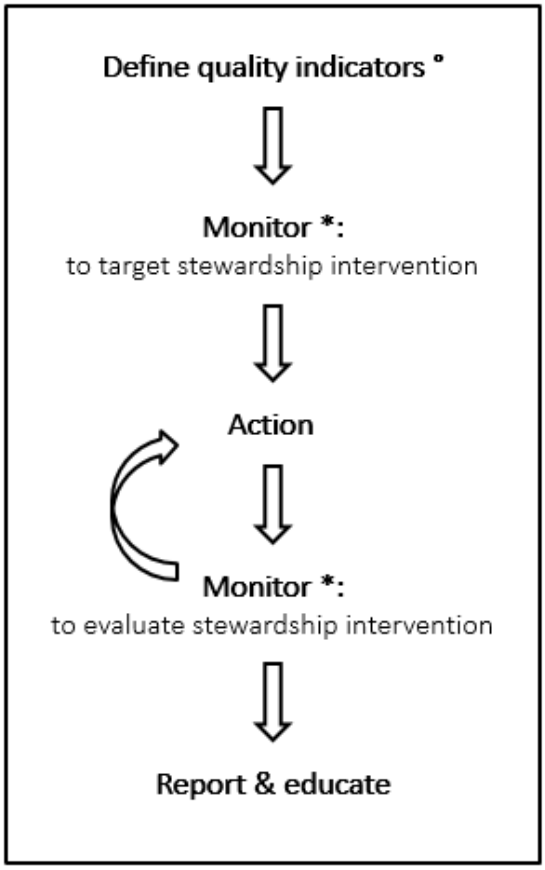

Figure 1: Implementation process of a stewardship intervention

°Quality indicators are defined as measures to assess a particular structure, process or outcome.[33, 34]

*Monitoring is defined as surveillance or tracking of antibiotic utilization, antimicrobial resistance patterns and infection rates.

C. ELECTRONIC SURVEILLANCE SYSTEMS

Monitoring is considered to be a core element of hospital ASP.[35, 36] Prior to the implementation of the electronic health record (EHR), dedicated personnel was trained and deployed to perform surveillance manually. It is evident that this approach is prone to human error. In addition, the surveillance process is complicated by the fact that conventional definitions used for manual chart review often include subjective criteria, leading to surveillance personnel inter-observer variability in sensitivity and specificity.[37-39] As traditional manual surveillance is time and resource consuming it is most often performed for a limited period in time and/or focused on specific types of infections, pathogens or patient populations.[40] Some major drawbacks are linked to this restricted surveillance strategy. Surveillance within narrow time frames for instance hampers the correct evaluation of stewardship actions, as effects can be directly related to the intervention or just reflect a seasonal trend.[41]

The computerization of administrative, microbiology, pharmacy and clinical data and the introduction of computerized physician order entry (CPOE) created new possibilities to support surveillance. In recent years, reports on a wide and very diverse range of electronic surveillance systems (ESS) have been published.[37, 38, 42-46] The majority of these systems are locally developed in-house ESS instead of commercially supplied software packages.[37] Consequently, an in-hospital validation of these systems is imperative. Considerable variation in sensitivity and specificity exists between different ESS. Performance depends on the source data that are being used and on the type of infection under study.

Experience has been gained with the use of many different types of data to support surveillance. Until now, administrative coding data (ACD) are probably the most frequently used data source as this information is already collected for other purposes such as coding and billing.[47] Unfortunately, ESS uniquely based on ACD have proven to be largely inaccurate, mainly because surveillance is not the primary objective of this registry and its validity depends largely on the precision of the information that is provided by the physician.[38, 45, 48] The importance of combining information from several data sources is increasingly recognized.[37, 46] Results from microbiology, biochemistry and antimicrobial prescription reports are quite easy to retrieve. The main challenge consists of picking up nuanced clinical diagnostic information from EHRs. Clinical data however have shown to outperform ACD.[49] In this respect, major progress has been made in the application of natural language processing tools to convert unstructured electronic patients charts to structured information, but additional research is needed to allow routine implementation of this technique for the purpose of surveillance.[46]

Until now, the majority of the ESS still focuses on selected types of infections. Most attention is devoted to infections that serve as a hospital quality indicator and/or are used for benchmarking e.g. central line-associated bloodstream infection (CLABSI), surgical site infection (SSI) and ventilator-associated pneumonia (VAP).[38] Consistently high sensitivity figures are reported in studies targeting bloodstream infections (BSI). ESS targeting infections, such as pneumonia, for which a diagnostic 'gold standard' is unavailable or depending on subjective diagnostic criteria perform substantially worse.[37]

ESS can be fully automated or require a certain amount of manual input. Some of the semi-automated systems use algorithms to detect potentially interesting cases that subsequently need detailed manual assessment.[50] Others depend on the (mandatory) input of clinical patient information by healthcare professionals.[51, 52] Fully and semi-automated systems each have their own advantages and drawbacks. Fully automated surveillance has evolved significantly over the last years, driven by an increasing demand for benchmarking and public reporting of infection rates and antibiotic consumption figures. Infections for which a set of clear, objective and electronically easy accessible diagnostic criteria is available e.g. a CLABSI, are an ideal target for fully automated ESS. Semi-automated systems on the other hand offer the possibility to capture more complex clinical info and steps of the diagnostic reasoning process which is often required to make the correct diagnosis of a complicated intra-abdominal infection or VAP.

Different strategies may underlie the case finding process of an ESS. The most frequently applied and best studied approach is the use of a computerized rule-based decision tree algorithm. As a rule, this strategy offers a dichotomous answer: infection is present or not. Complex infections are more difficult to capture by these static algorithms.[53] An alternative approach based on multivariable regression modelling was examined for CLABSIs, SSI and drain-related meningitis.[54] This method relies on the construction of a model which weighs individual predictors from multiple data sources to generate a prediction of the presence of an infection. As such, manual chart review can be limited to those patients that are identified as having a high probability of infection. Sensitivity and specificity of the model can be altered by selection of different probability cut-offs. Further research on the application of this technique is mandatory. A myriad of other strategies, such as machine learning techniques, are under investigation and the number of reports on this subject is growing steadily.[55-58]

Most ESS use traditional diagnostic criteria to construct their case finding strategy. The increasing demand for inter-hospital comparison initiated some changes in the field of surveillance over the last few years.[38] For instance, to bypass the problem of interrater variability in the traditional diagnostics of VAP, a new definition using exclusively electronically available data has been created.[59-63] This new concept of ventilator-associated events (VAE) is

accepted by the Centers for Disease Control and Prevention - National Healthcare Safety Network (CDC-NHSN).[64] Multiple reports with conflicting results on the reliability and usefulness of this 'synthetic' definition have been published in recent years.[65-67]

In conclusion, implementation of an ESS has shown to be feasible, provide accurate results and save time. However, we still have a long way to go before manual surveillance will be fully replaced by its electronic counterparts. Some important prerequisites to promote the chances of a successful implementation of an ESS need to be addressed. These components are summarized in table 1.[37, 38, 44, 68]

1. Involvement of healthcare practitioners* in the design
2. Standardization of data collection
3. Incorporation of surveillance in daily workflow
4. Timely reporting of results to healthcare practitioners
5. General applicability - transferability to other hospitals

Table 1: Prerequisites for successful implementation of an electronic surveillance system

*e.g. physicians (including clinical microbiologists), pharmacists and infection control practitioners

“The most profound technologies are those that disappear. They weave themselves into the fabric of everyday life until they are indistinguishable from it.”

Marc Weiser

2 COSARA

The most severely ill patients are monitored and treated in the ICU. Complex and/or urgent, but nonetheless well-balanced and accurate actions are often imperative. Information technology (IT) is considered to be an efficient tool supporting daily clinical decisions in the data-rich critical care environment.[69-71] The implementation process of an Intensive Care Information System (ICIS) was initiated in May 2003 in the ICU of the Ghent University Hospital. From that moment on large amounts of patient monitoring and observational data are being collected and stored at the point of care, supplemented by data derived from multiple bedside medical devices. In addition, this specialized ICU software allows CPOE and computerized medication administration recording. As such, an overabundance of digital information became readily available which created new challenges and opportunities.

A. DESIGN OF A DATA VISUALIZATION DASHBOARD ON INFECTION

As more patient related information is currently offered in an electronic format, physicians can rely on a more comprehensive and complete set of data when making treatment decisions. However, the process of mental data aggregation is often a time-consuming cognitive challenge as, depending on the specific clinical question that is being addressed, the required info is scattered across multiple data sources. Clinical dashboards are increasingly being adopted as means to assist physicians in specific task oriented data integration. The dashboard principle originated in the management sector and was subsequently introduced in healthcare.[72, 73] This visualization tool supports easy access to timely and relevant clinical information in a concise, visually attractive and user-friendly format.[74] Although this field of research is still in his infancy, a growing number of reports supporting the use of clinical dashboards has been published.[73, 75-79]

Considering the central and complex role of infection management in ICU patients, the option to design a data visualization dashboard on infection management was explored in our ICU. The first brainstorming sessions between ICU healthcare workers and software engineers from the Department of Information Technology (INTEC) of the Faculty of Engineering of Ghent University, took place in 2005. The project was named COSARA: 'Computer-based Surveillance and Alerting of nosocomial infections, Antimicrobial Resistance and Antibiotic consumption in the ICU'. Financial support from the Institute for the Promotion of Innovation through Science and Technology in Flanders was awarded in 2007. The concept of COSARA was refined through

multiple multidisciplinary meetings and resulted in the implementation of the software in 2009. COSARA received a thorough makeover in 2011 and was converted from a desktop program to a web application. Shortly thereafter, this COSARA 2.0 version was implemented in Antwerp University Hospital. In doing so, it was demonstrated that the software could be made compatible with various ICIS, laboratory and X-ray systems. The next important step was taken in 2014 with the introduction of COSARA in the pediatric ICU of Ghent University Hospital. Compared to the adult population, infections in critically ill children are more often viral of nature and anti-viral therapy is not always required. As the identification of an infection by COSARA is triggered by the initiation of antibiotic treatment (see below), some adjustments to the software were needed to capture information regarding these viral infections in the pediatric population correctly. The latest version of COSARA was launched in 2016. The COSARA 2.5 version was created to run on mobile devices to promote its use during ward rounds. Figure 2 shows in more detail the COSARA design and implementation timeline.

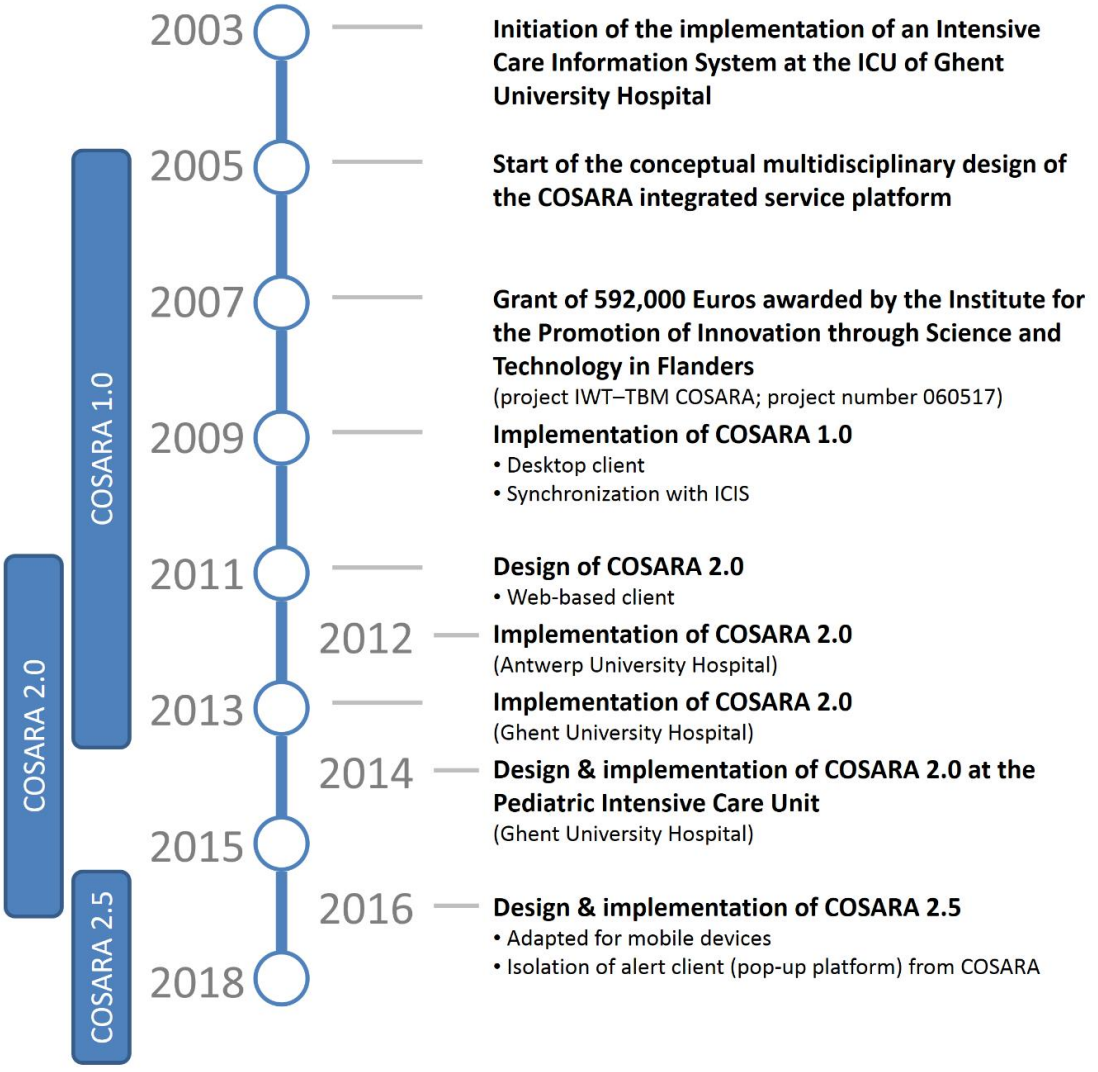

Figure 2: COSARA design and implementation timeline

ICU: intensive care unit; ICIS: intensive care information system

The cornerstone of the COSARA software is a central infection dashboard view which is built up around a timeline (figure 3). Infection related patient data from distributed stand-alone vendor specific systems (ICIS, laboratory reports and X-ray images) are merged through the software, aiming to minimize navigation. Real-time synchronization with the individual systems ensures the presentation of up-to-date information. Time-graphs at the top of the page show the evolution of selected clinical (e.g. fever) and laboratory (e.g. leukocytosis, CRP) variables and indicators of severity-of-illness (e.g. the arterial oxygen tension (PaO_2)/ fractional inspired oxygen (FiO_2) ratio, sequential organ failure assessment score (SOFA)). For every antibiotic prescription that is entered via CPOE, a horizontal bar is created that runs just above the timeline and lengthens upon duration of the prescription. This bar is accompanied by a second bar running in parallel below the timeline and describing the indication for this antibiotic (introduced manually and structured: see below). More detailed information on prescription and infection are revealed on the base of the screen by hovering over the bars. All positive microbial culture results and matching susceptibility patterns are automatically indicated above the timeline using small symbols, whereas selected microbiological isolates that are linked to an infection are displayed underneath the timeline. Additional tabs within the selected case file present identical information in an alternative format (e.g. microbiology, antibiotic-infection combinations) (figure 4 and 5) or supplementary data (e.g. catheter information, consecutive chest X-rays) (figure 6).

As such, a more holistic perspective on a complex history in a patient with a long ICU stay involving multiple infectious episodes and antibiotic treatments, is presented to the physician. A valuable insight into difficult patient files may facilitate the decision-making process during ward rounds and interdisciplinary staff meetings with microbiologists and infectious diseases specialists. In addition, the graphically attractive overview assists shift reports and teaching opportunities for junior staff and trainees.

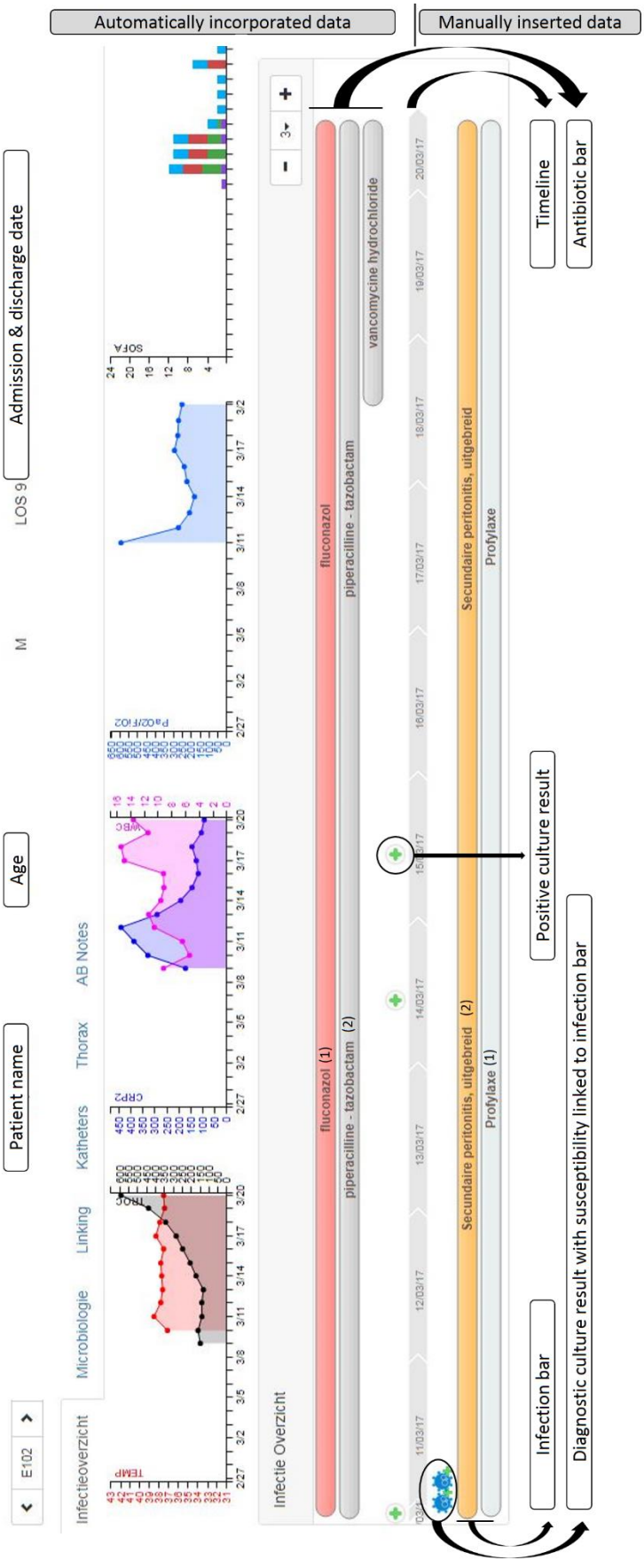

Figure 3: COSARA central infection dashboard view

Figure 4: COSARA microbiology overview

Figure 5: COSARA antibiotic-infection combinations linked to microbiology data

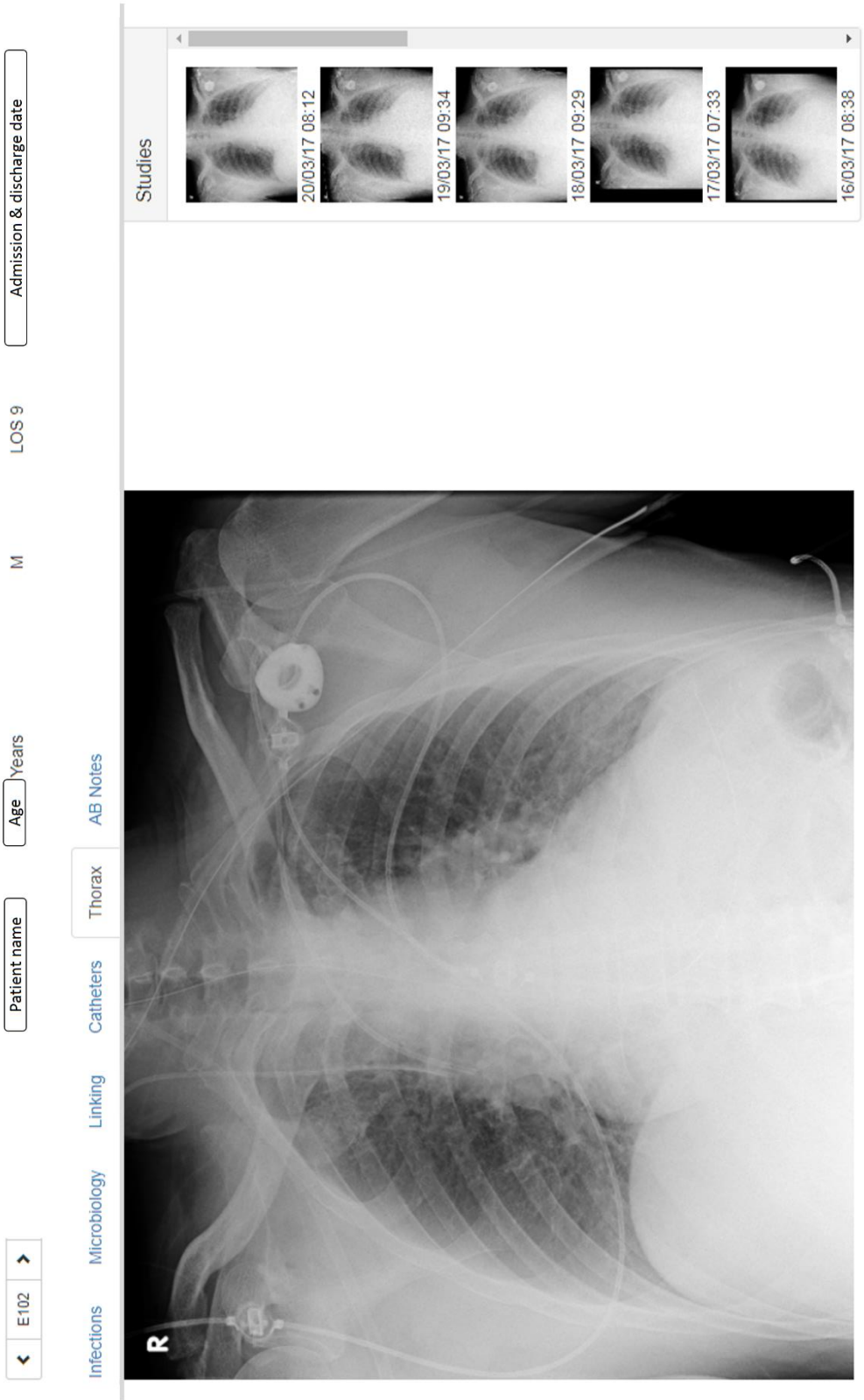

Figure 6: COSARA consecutive chest X-rays

B. REAL-TIME MAPPING OF THE ANTIBIOTIC DECISION-MAKING PROCESS

The antibiotic treatment decision-making process is often influenced by multiple factors. As a rule this information is not or incompletely recorded in the patient's file, which complicates retrospective reconstruction of this process. The ambition to capture the physician's motivation at the time of a new antibiotic prescription was incorporated in the basic structure of the COSARA software and makes it unique in its kind. The infection bar in the overview is fed by data from a short questionnaire that 'pops up' in real-time after each electronic antibiotic prescription and inquires the prescriber about indication, likely focus and severity of infection and the presence of microbiological data guiding the antibiotic choice. This survey is self-explanatory and requires only a limited time investment (less than one minute) (figure 7). The resulting preliminary infection bar can be altered manually during the course of the infection when more data concerning the origin and clinical evolution of the infection become available. Additionally, more details on the infection focus can be added and stored as structured data (figure 8).

Figure 7 a: COSARA pop-up questionnaire

Figure 7 b: COSARA pop-up questionnaire

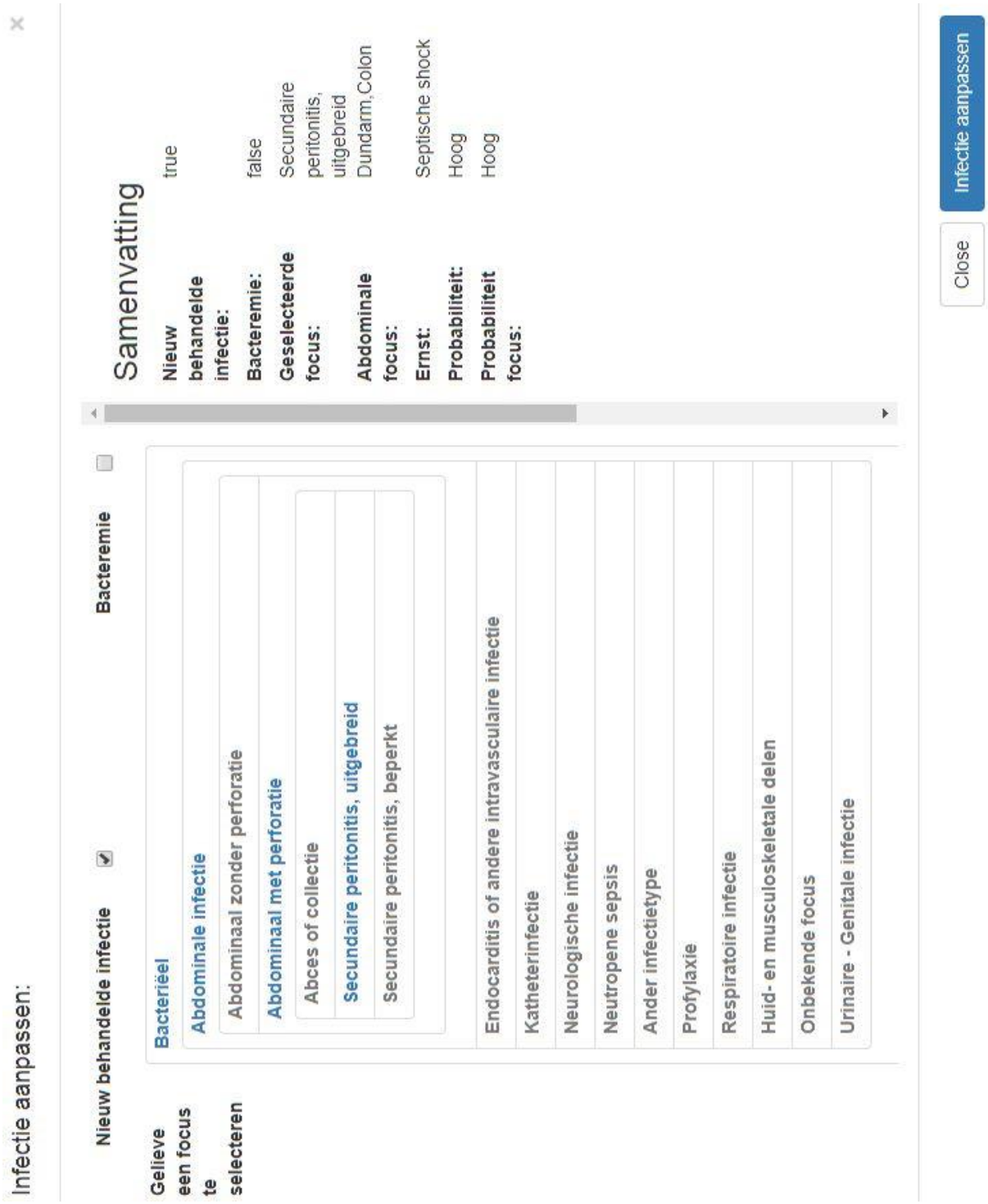

Figure 8: COSARA insertion of structured data on the infection focus

C. CONSTRUCTION OF A RELATIONAL DATABASE ON INFECTION

As outlined in the previous paragraphs, COSARA integrates patient and infection related data from different electronic sources. The data visualization dashboard promotes information management and enables manual linking of microbiology data to antibiotic-infection combinations. Microbial pathogens may be designated as causative pathogens, or as non-causative pathogens influencing antibiotic prescription (e.g. nasal carriage of methicillin-resistant *Staphylococcus aureus* promoting glycopeptide prescription in suspected pneumonia with negative sputum cultures). Merging of antibiotic, clinical diagnostic and microbiology data can be performed during clinical workflow or at any later stage. To ensure high quality data, the COSARA dashboard of every individual patient admitted to the ICU is reviewed and completed following ICU discharge by designated users.

The continuous data merging results in the built-up of a large relational database. This data warehouse can be consulted for multiple purposes e.g. clinical research, management, surveillance and education. A distinct module in the software allows real-time assessment of a vast array of predefined analyses by physicians. Until now, assistance of an IT specialist is required to extract the raw data. The architecture of the database, however, permits physicians to execute comprehensive and complex analyses autonomously by linking of these extracted data.

3 STUDY OUTLINE

A. USE OF A COMPUTER-ASSISTED REGISTRATION PROGRAM TO FACILITATE SURVEILLANCE IN THE ICU

Documentation of infections is a crucial step in the implementation process of an ASP (figure 1).[35, 36] COSARA is designed to facilitate prospective collection of infection related information as structured data. Assessment of the validity of COSARA as an infection surveillance tool and the feasibility to perform registration in a continuous way was deemed essential. In a first study, traditional manual paper-based surveillance (PBS) was compared with computer-assisted surveillance (CAS) by means of COSARA for ICU-acquired respiratory tract, urinary tract and bloodstream infections during a four-month period (November 1st 2011 –February 29th 2012). A formal checklist based on CDC-NHSN criteria to document infection was used by PBS, whereas CAS assigned diagnoses based on a clinical estimation of the probability of infection by the physician. Overall agreement between both surveillance methods was measured. Conflicting results were reviewed by an independent panel of physicians. Additionally, the time investment of both surveillance methods was recorded in order to evaluate feasibility of long-term prospective surveillance.

B. INVESTIGATION OF ANTIBIOTIC PRESCRIPTION AND ANTIBIOTIC RESISTANCE IN THE ICU TO SUPPORT THE DESIGN OF AN ASP

The collection of high quality surveillance data primarily serves a higher purpose, in particular, the design of an ASP and ultimately the improvement of bedside clinical care. Data acquisition for the following studies was performed through the use of COSARA.

3.B.1 A complete and multifaceted overview of antibiotic use and infection diagnosis in the ICU

As mentioned previously, comprehensive longitudinal data on antimicrobial management in the ICU are currently lacking. Details on prescription indications are often insufficiently captured as this process is considered too time and resource consuming. To the best of our knowledge, the basic principle of COSARA (which is the continuous prospective merging of antibiotic, clinical and microbiology data) has not been applied elsewhere. This approach has resulted in the prospective building up of an extensive database since the implementation of COSARA. A descriptive analysis of a dataset covering four years of surveillance thus enables a unique presentation on global antibiotic utilization, infection epidemiology and microbiology in our ICU. As such, we tried to get a bird's eye view of our local antibiotic prescribing practices. We aimed to provide a starting point for the design of an ASP based on an evaluation of the infection probability (high/moderate/low) that was assigned to all therapeutic prescriptions.

3.B.2 Empirical antibiotic prescription in hospital-acquired pneumonia and the added value of the use of surveillance cultures

Hospital-acquired pneumonia (HAP) is defined as pneumonia occurring 48 h or more after hospital admission. VAP is a subgroup of HAP, developing in mechanically ventilated patients 48 h or more following endotracheal intubation.[80] HAP is considered as one of the most important hospital-acquired infections in terms of prevalence, morbidity, mortality and use of resources.[81, 82] HAP is a major driver for antibiotic consumption in the ICU and as such also an important stewardship target. Up until now microbiology turnaround time for respiratory samples is 48 h, subsequently the initial antibiotic treatment choice is as a rule empirical.[82] To ensure early appropriate therapy, the use of broad-spectrum antibiotic therapy is advocated in international guidelines.[17] It is recommended to adjust this antibiotic regimen to local antibiotic resistance data. In addition, treatment selection should be guided by the patient's severity of illness and risk for involvement of MDR pathogens. Surveillance cultures (SC), which are cultures taken at

ICU admission and further at regular intervals during ICU stay, contribute to a better knowledge of the patient's colonization status.[83] The use of these SC to improve empirical antibiotic choice and restrict superfluous broad-spectrum agents has extensively been studied over the last years, but remains a matter of debate.[84-89]

In Ghent University Hospital ICU, the selection of an empirical HAP treatment is not guided by formal algorithms. By retrospective evaluation of all HAP episodes in the period from July 1st 2009 to October 31st 2012 we assessed the potential impact of the implementation of a treatment algorithm on appropriateness and spectrum of the proposed treatment strategy. Two different algorithms were constructed. A local ecology-based algorithm (LEBA) takes previously recorded local resistance patterns into account combined with patient related characteristics e.g. severity of illness and clinical risk factors for MDR colonization. A surveillance culture-based algorithm (SCBA) assessed the added value of the incorporation of information from systematically collected SC to guide empirical antibiotic choice.

3.B.3 Local antibiotic de-escalation practices and impact on the emergence of antibiotic resistance

Over the last decades, de-escalation has been a widely recommended and commonly applied stewardship strategy.[90, 91] Empirical broad-spectrum combination therapy, initiated to cover all potential causative pathogens, is streamlined as soon as more information on infection probability, clinical course and causative microbiology becomes available. De-escalation is still not well-defined. It may consist of replacement of broad-spectrum drugs by more narrow-spectrum agents, stopping one or more components of a combination therapy, limitation of treatment duration or discontinuation of all antimicrobial agents in the absence of an infection.[92-94] A reduction in overall broad-spectrum antibiotic consumption and MDR emergence is pursued. Intuitively, de-escalation is a very attractive stewardship action harmonizing early appropriate therapy with restriction of the unfavorable effects of antimicrobial treatments. Unfortunately, large-scale, high quality data supporting a positive clinical and ecological outcome are lacking.[93, 95, 96]

To gain more insight into our local de-escalation practices we analyzed all beta-lactam antibiotic courses of at least 48 h duration that were prescribed as first line treatment for an infection between January 1st 2013 and December 31st 2014. Frequency and determinants for de-escalation (and escalation) of therapy were assessed. Subsequently, we evaluated the effect of de-escalation on patient outcome. We focused on the emergence of antibiotic resistance following different treatment strategies, a previously insufficiently explored study domain. The

availability of routine SC in our ICU population combined with our COSARA dataset, offered the opportunity to assess:

- The emergence of resistance to the initially prescribed beta-lactam antibiotic
- The emergence of MDR pathogens

3.B.4 Facilitation of internal stewardship decision-making: identification of potentially unjustified prolonged antibiotic treatment courses

The systematic assessment of the ongoing need of an antibiotic treatment 48-72 h following its initiation is considered a core action of ASP. A drill-through-to-detail analysis on the aforementioned dataset covering four years of surveillance (section 3.B.1) was performed to illustrate the potential of our surveillance method to make an estimate of the effect of such a stewardship intervention. Three 'last resort' antibiotic classes for which a prudent use is recommended (carbapenems, glycopeptides and oxazolidinones) were assessed. We identified prescriptions of these three antibiotic classes which were sustained more than 3 days of therapy without clear clinical or microbiological justification. We calculated the potential saving in antibiotic consumption by an antibiotic time out for each of these antibiotic agents.

4 ORIGINAL STUDIES

A. VALIDITY ANALYSIS OF A UNIQUE INFECTION SURVEILLANCE SYSTEM IN THE INTENSIVE CARE UNIT BY ANALYSIS OF A DATA WAREHOUSE BUILT THROUGH A WORKFLOW-INTEGRATED SOFTWARE APPLICATION

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4.A.1 Abstract

Background:

An electronic decision support program was developed within the intensive care unit (ICU) that provides an overview of all infection-related patient data, and allows ICU physicians to add clinical information during patient rounds, resulting in prospective compilation of a database.

Aim:

To assess the validity of computer-assisted surveillance (CAS) of ICU-acquired infection performed by analysis of this database.

Methods:

CAS was compared with prospective paper-based surveillance (PBS) for ICU-acquired respiratory tract infection (RTI), bloodstream infection (BSI) and urinary tract infection (UTI) over four months at a 36-bed medical and surgical ICU. An independent panel reviewed the data in the case of discrepancy between CAS and PBS.

Findings:

PBS identified 89 ICU-acquired infections (13 BSI, 18 UTI, 58 RTI) and CAS identified 90 ICU-acquired infections (14 BSI, 17 UTI, 59 RTI) in 876 ICU admissions. There was agreement between CAS and PBS on 13 BSI (100 %), 14 UTI (77.8 %) and 42 RTI (72.4 %). Overall, there was agreement on 69 infections (77.5%), resulting in a kappa score of 0.74. Discrepancy between PBS and CAS was the result of capture error in 11 and 14 infections, respectively. Interobserver disagreement on probability (13 RTI) and focus (two RTI, one UTI) occurred for 16 episodes. The time required to collect information using CAS is less than 30% of the time required when using PBS.

Conclusion:

CAS for ICU-acquired infection by analysis of a database built through daily workflow is a feasible surveillance method and has good agreement with PBS. Discrepancy between CAS and PBS is largely due to interobserver variability.

4.A.2 Introduction

Intensive care unit (ICU)-acquired infection is a frequent complication in patients admitted to the ICU,[97, 98] and is associated with adverse outcomes.[99, 100] Although the incidence of ICU-acquired infection varies according to the patient case-mix, it is, to some extent, a preventable complication. Surveillance of various types of infection has been advocated as a means to measure hospital quality, and serves as an instrument to guide and evaluate the infection control policy.[101] However, conventional surveillance requires time-consuming extraction of data from dispersed information sources by dedicated and trained personnel. The cost and workload associated with conventional surveillance is a major barrier to its continuous implementation; as such, surveillance is generally performed erratically or for limited time periods. In a joint project with the Department of Information Technology of Ghent University, the authors designed and implemented a software application for electronic decision support in infectious diseases at the ICU [Computer-based Surveillance and Alerting of infections, Antimicrobial Resistance and Antibiotic consumption in the ICU (COSARA)]. COSARA has been fully operational since 2010 at the study ICU, where it assists the attending ICU physician in acquiring oversight of various data related to infection diagnosis and treatment. The program facilitates the compilation of an extensive data warehouse on antibiotic use and infection in the ICU, which can be consulted for various purposes.[102] It was hypothesized that analysis of the COSARA data warehouse would facilitate surveillance of ICU-acquired infection, and the list of infections resulting from conventional prospective paper-based surveillance (PBS) was compared with the list of infections retrieved from COSARA [computer-assisted surveillance (CAS)]. For the purpose of this study, surveillance was restricted to ICU-acquired respiratory tract infection (RTI), urinary tract infection (UTI) and bloodstream infection (BSI).

4.A.3 Materials and methods

The study was conducted at the 14-bed medical ICU (MICU) and the 22-bed surgical ICU (SICU) of Ghent University Hospital (1050 beds). The MICU and SICU are completely computerized, and COSARA software has been available on every personal computer dedicated to patient care since 2010. With COSARA, all infection-related data from the various electronic patient records are integrated and presented to the treating ICU physician by means of a continuously updated clinical dashboard. This includes a graphical display of current and past antibiotic treatments as a timeline, and provides direct links to a real-time copy of the various source records. The graphical interface allows episodes of antibiotic treatment to be labelled according to a predefined list of indications and diagnoses, and linked with microbiological culture results. Labels are made in a two-step approach: a preliminary label is created by completing a short

questionnaire that pops up at the time of electronic prescription; and a definitive label can be assigned after review of all relevant data. This can be done during clinical patient rounds, interdisciplinary staff meetings or at any given time. All data are stored in a data warehouse.

The study was approved by the institutional ethics committee. Only patients aged 16 years or more were included. All patients and relatives were informed about the surveillance through a leaflet distributed at ICU admission, which explicitly offered the possibility to opt-out of the study.

Design

The results from CAS were compared with those from PBS over a four-month study period (1st November 2011-29th February 2012). It was estimated that four months of surveillance would allow the inclusion of 100 infections, based upon average observed incidence rates at the study ICU [RTI (N=15/1000 ICU-days), UTI (N=5/1000 ICU-days) and BSI (N=5/1000 ICU-days)] found by previous surveillance in collaboration with the national Scientific Institute of Public Health. An infection was defined as ICU-acquired if it occurred 48 h or more after admission to the ICU. Infections diagnosed at re-admission of a patient who was discharged from the ICU less than 48 h previously were also considered to be ICU-acquired. Only the first infectious episode was included for patients who developed consecutive infections during the same ICU stay. Results of CAS and PBS were compared with a reference set to determine sensitivity and specificity (see below). The time required for data collection using both surveillance systems was recorded per week.

Paper-based surveillance

One of the investigators (GD) screened all ICU patients for the presence of ICU-acquired infection three times per week. GD was blinded to the COSARA graphical display, but had access to all electronic source data and was allowed to contact the treating physician for more information if necessary. The starting point for detection of a potential case of BSI, UTI or RTI was the presence of a pathogenic micro-organism in a blood, urinary or respiratory culture, respectively. In addition, the patient's electronic medical record was screened to detect episodes of clinically suspected RTI treated with antibiotics in the absence of microbiological documentation to ensure completeness of the dataset. PBS used formal checklists that were developed based on Centers for Disease Control and Prevention-National Healthcare Safety Network (CDC-NHSN) criteria,[103] and modified to make them applicable to the ICU patients as described below.

A BSI was defined as the presence of a pathogen (excluding common skin contaminants) in at least one blood culture. The presence of common skin contaminants in at least two blood cultures drawn on separate occasions, together with fever, chills or hypotension, and judged to require antimicrobial treatment by the ICU physician was defined as ICU-acquired BSI.

Urinary cultures were performed quantitatively three times per week on a regular basis as part of the surveillance program. Symptoms of suprapubic tenderness or dysuria were not considered for UTI as these are difficult to assess in ICU patients.[104] UTI was defined as episodes of sepsis, pyuria (>25 white blood cells/mm^3), a positive urinary culture [growth of a uropathogen ≥ 10^5 colony-forming units (cfu)/mL], and judged to require antibiotic therapy by the treating physician. All episodes with a positive urinary culture that did not fulfill all of the criteria were considered as asymptomatic bacteriuria and were not retained. Episodes of UTI with the same pathogen growing in urinary and blood cultures were classified as UTI.

Clinical and radiological criteria for RTI conform with CDC-NHSN definitions.[103] CDC-NHSN diagnosis of microbiologically confirmed pneumonia relies on invasive sampling such as bronchoalveolar lavage (BAL) or protected specimen brushing. However, in the study hospital, microbiological analysis of respiratory samples routinely consists of semi-quantitative culture of blind end tracheal aspirate (ETA) in the ventilated patient or sputum in the non-intubated patient. For logistical reasons, BAL is not performed systematically in patients with a clinical suspicion of pneumonia, similar to current practice in the majority of ICUs.[105] It has been shown previously that quantitative and semi-quantitative culture results of BAL and ETA were concordant in a cohort of patients with suspected ventilator-associated pneumonia (VAP). Positive and negative predictive values of a semi-quantitative score of 1+ growth of a pathogen in ETA to identify the same pathogen in at least 10^4 cfu/mL in BAL were 81% and 87%, respectively.[106] Consequently, microbiologically confirmed pneumonia was defined as 1+ growth or more of a potential pathogen in ETA in the case of VAP, or in a purulent sputum sample of good quality (defined as less than three squamous epithelial cells per low power field) in the case of hospital-acquired pneumonia. Episodes of pneumonia complicated with BSI were classified as RTI.

Computer-assisted surveillance

Labelling of antibiotic indications and infections in the clinical dashboard was undertaken as part of daily routine clinical work and reflected the clinical opinion of the treating physician. The clinical dashboard was completed and supervised by two investigators [LDB (SICU) and PD (MICU)] during clinical rounds and interdisciplinary staff meetings. While the PBS checklist was not formally used as such, an estimation of the probability of infection (high/moderate/low) was

entered by consensus and using the same clinical, radiological and microbiological criteria as in the PBS. RTI was considered to be highly probable in the case of presence of a new or worsening infiltrate on chest X-ray, together with clinical signs of sepsis and new respiratory symptoms (increased sputum, increased purulence of sputum, worsening oxygenation), and a semi-quantitative score of 1+ growth or more of a pathogen in a good-quality respiratory sample. RTI was considered to be moderately probable in the case of all previous criteria but in the absence of respiratory pathogens or growth below the threshold of 1+. UTI was considered to be moderately probable in the case of pyuria and sepsis, other foci of infection being unlikely, and the presence of a urinary pathogen in ≥ 10^5 cfu/mL. Highly probable UTI required isolation of the same pathogen in blood and urinary cultures. BSI was defined by the same criteria as in PBS; episodes with coagulase-negative staphylococci alone were considered to be moderately probable, and episodes with pathogenic bacteria were considered to be highly probable. By querying the COSARA data warehouse, all episodes from the study period that were labelled as RTI, BSI or UTI with high or moderate probability and a start date beyond 48 h of ICU admission were retrieved as ICU-acquired infection.

Reference set

All episodes of ICU-acquired infection that had discordant results on CAS and PBS were reviewed independently by a senior microbiologist/infection control practitioner (ILR) and a senior ICU physician (JD), using the PBS criteria as described previously. Reasons for disagreement between CAS and PBS were discussed. Episodes with concordant results and those retained after independent review comprised the reference set.

Statistical analysis

All data are presented as absolute numbers with or without percentages. All statistical analyses were performed using Statistical Package for the Social Sciences Version 21 (SPSS Inc., Chicago, IL, USA). Kappa measures of agreement were calculated. As universally accepted guidelines do not exist, the guidelines of Fleiss were adopted (kappa ≥0.75, excellent agreement; kappa >0.4 and <0.75, fair to good agreement; kappa <0.4, poor agreement).[107, 108]

4.A.4 Results

Comparison of CAS and PBS

PBS identified 89 ICU-acquired infections and CAS identified 90 ICU-acquired infections in 876 ICU admissions. The results are shown in Table 2. Overall, CAS agreed with PBS on 69 infections (77.5%), resulting in kappa = 0.74. Agreement was lower for RTI (kappa = 0.70) than for BSI (kappa = 0.96) and UTI (kappa = 0.80).

Table 2: ICU-acquired infections identified by paper-based surveillance (PBS) and computer-assisted surveillance (CAS)

Type of infection	Cases identified by PBS	Cases identified by CAS	Proportion of infections identified by PBS, which are also identified by CAS (%)
BSI	13	14	13/13 (100%)
UTI	18	17	14/18 (77.8%)
RTI	58	59	42/58 (72.4%)
All infections	89	90	69/89 (77.5%)

BSI= bloodstream infection, RTI= respiratory tract infection, UTI= urinary tract infection

Comparison of CAS and PBS with the reference set

The reference set comprised 99 ICU-acquired infections: 14 BSI, 65 RTI and 20 UTI, corresponding to a cumulative incidence of 1.6 cases per 100 ICU admissions for BSI, 7.4 cases per 100 ICU admissions for RTI and 2.3 cases per 100 ICU admissions for UTI. Overall sensitivity and specificity were 89% and 100%, respectively, for PBS, and 81% and 99%, respectively, for CAS. Test characteristics by infection type are shown in Table 3.

Table 3: Test characteristics of paper-based surveillance (PBS) and computer-assisted surveillance (CAS) as compared to the reference set

Type of ICU-acquired infection	Sensitivity,%	Specificity, %
BSI - PBS	93	100
BSI - CAS	100	100
RTI - PBS	88	99.9
RTI - CAS	77	99
UTI - PBS	90	100
UTI - CAS	80	99.9

BSI= bloodstream infection, RTI= respiratory tract infection, UTI=urinary tract infection

PBS was more prone to human error than CAS (11 vs 4). However, more technical problems were encountered with CAS, including failure to store antibiotic episodes (N = 5) and query errors (N = 5). However, for the greater part, discordant results between conventional PBS and CAS were the consequence of interobserver variability. Reasons for disagreement between the two surveillance methods are shown in Table 4.

Assessment of time expenditure

Manual PBS data collection required a mean time investment of approximately 7 h/week. The average time spent, in total, by the supervisors in charge of updating the COSARA graphical platform was 2 h/week.

Table 4: Reasons for discrepancy between paper-based surveillance (PBS) and computer-assisted surveillance (CAS)

	False negative episodes		**False positive episodes**	
	PBS	CAS	PBS	CAS
Capture error	1 BSI, 6 RTI, 1 UTI missed at screening	1 RTI, 2 UTI wrong labelling in clinical dashboard	-	1 RTI: wrong labelling in clinical dashboard
	2 RTI, 1 UTI screened but erroneously discarded (notification error)	5 RTI: not stored in data-warehouse		2 RTI, 1 UTI: falsely retrieved by query
		1 RTI, 1 UTI: not retrieved by query		
Interobserver variability	-	6 RTI: PBS criteria met, classified as low probability by CAS	1 RTI: PBS criteria not met when reassessed	6 RTI: PBS criteria not met, considered as clinically significant infection by CAS
		2 RTI, 1 UTI: PBS criteria met, assigned to other infection focus by CAS		

BSI= bloodstream infection, RTI= respiratory tract infection, UTI=urinary tract infection

4.A.5 Discussion

Good agreement was found between CAS for ICU-acquired infection conducted through analysis of the COSARA data warehouse and conventional, prospective PBS. CAS and PBS methods concurred with an overall kappa score of 0.74 for RTI, BSI and UTI.

The approach used in this study is one of the various forms of CAS that have been developed thanks to the advanced computerization of medical data, in order to facilitate the time-consuming process of PBS. Distinction can be made between fully or partially automated tools, depending on whether they replace or assist healthcare personnel in the act of surveillance. Fully automated tools rely on computer programmes retrospectively combing through microbiological data, administrative records, pharmacy data or a combination of these to capture key indicators of infection. While screening diagnostic codes is the most simple and straightforward electronic method of identifying infection, it has been shown to be largely inaccurate.[109-111] To improve sensitivity and specificity, more complex algorithms have been developed that combine different sets of data or sieve through the captured episodes with additional filters.[43, 112] In contrast, CAS, as performed in this study, can be classified as partially automated as it requires a substantial input of interpretative information. With COSARA, the automated collection of infection-related data from various electronic sources in a single data warehouse is complemented by prospective manual insertion of medical diagnoses as structured data. Partially automated methods are based upon the assumption that the comparison of parameters and data against predefined sets of criteria by a computer programme may support but not fully replace the complex human reasoning involved in making a diagnosis such as that of an infection.[113] This has been corroborated by the results of a study by Steinmann et al.,[114] where ward physicians not only had to fill in clinical parameters on a daily basis to feed a programme for electronic infection registration, but were also invited to give a personal opinion on the presence or absence of infection. The fully automated registration resulting from comparison of these clinical parameters with predefined criteria for VAP showed relatively poor agreement with the physician's evaluation for pneumonia, as reflected by a kappa score of 0.49. This was essentially due to low specificity of the automated system, and illustrates that automated identification of infection based upon raw clinical data may lead to over-diagnosis, unless reviewed by ICU physicians or infection control practitioners.[114]

Case finding is a critical step within partially automated methods that determines sensitivity of the surveillance method. With COSARA, a treatment-based selective surveillance approach was used, with potential cases identified by the presence of an electronic antibiotic prescription. Consequently, infections for which no antibiotic therapy was initiated were not recorded. It is postulated that the number of these is very low under the assumption that a diagnosis of

clinically relevant infection very likely implies antimicrobial therapy in the absence of do-not-resuscitate codes. Specificity of treatment-based case selection depends on the efforts made to distinguish between likely infection and prolonged empirical antimicrobial therapy for non-infectious conditions. In this application, all antibiotic prescriptions were re-assessed and linked with microbiological culture results, and received a final classification by ICU physicians involved in daily care. In a study comparing different methods of CAS, a method selecting cases upon antibiotic prescription had sensitivity of 82% and specificity of 67%; filtering these cases for the presence of a positive microbiological culture result increased specificity to 87%.[115]

The validity of CAS programmes is usually assessed by comparison with traditional PBS. However, as illustrated by other analyses and the present study, it is clear that PBS is not 'set in stone', as it is subject to screening failure and interobserver variability.[60, 116-118] In order to enable a less biased calculation of the test characteristics of both CAS and PBS in the absence of a true gold standard test, a reference set serving as a surrogate gold standard was constructed. Cases on which both surveillance methods agreed were not re-evaluated by the independent panel; this is a limitation of this approach, as this could have influenced sensitivity and specificity analyses. However, it is believed that the number of episodes of ICU-acquired infection missed by both methods, and the number of false-positive registrations of ICU-acquired infection by both methods, are fairly low. Interobserver variability was found to account for most of the discrepancy between the two methods. This was most pronounced for RTI; a finding which is in accordance with the literature and can be explained by the inaccurate diagnosis of RTI in critically ill patients, involving many subjective components and non-specific clinical, radiological and biochemical signs.[60] This insight has led the CDC to modify the 2008 NHSN definitions, proposing a novel algorithm based on more objective criteria and amenable for automatic processing; however, these new criteria need further validation.[62] Interobserver variability may have been increased by the design of the study, as the PBS investigator used a more rigid checklist whereas the CAS investigators applied clinical judgement. The CAS investigators were deliberately asked to use clinical appreciation to stay as close as possible to routine clinical work. Application of the CDC-NHSN criteria may allow better comparison between centres, but at the expense of producing results that deviate from what is perceived or present in reality.

With increasing public awareness of healthcare-associated infection as an adverse event related to healthcare delivery, the pressure to provide continuous surveillance data is growing stronger. In addition, as increasing antibiotic resistance requires more judicious use of currently available antibiotics, managing antibiotic prescription within the ICU has become a priority. CAS as supported by electronic decision programmes such as COSARA offers a number of opportunities.

Regular queries of the data warehouse may enable the identification of outbreaks, observation of trends in antibiotic consumption, and evaluation of the effect of targeted interventions. Depending on local hospital organization and staffing, supervision of the COSARA graphical platform and ultimate labelling of infections can be performed by any professional engaged in infection control. In COSARA, the presentation of all clinical, microbiological and radiological data on a single platform facilitates the use of different criteria, including the CDC-NHSN criteria for labelling the infectious episodes, depending on the purpose of the surveillance. Stricter use of criteria is preferable for benchmarking or comparison between ICUs, while less stringent surveillance that reflects clinical practice more closely serves best to analyse antibiotic use or evaluate the effect of interventions.

Drawbacks of COSARA include the aforementioned omission of infections for which no antibiotics are prescribed, and a reliance on healthcare workers to complete diagnostic labels, which may lead to human errors such as incomplete recording or mislabelling. Finally, as this was a single-centre study, it is possible that the good performance of CAS by COSARA is linked to the characteristics of the particular clinical patient information system in use. However, the authors are currently deploying COSARA in another tertiary hospital ICU that uses a different clinical information system.

In summary, CAS for ICU-acquired infection by analysis of the COSARA data warehouse has good agreement with PBS, and required less than one-third of the time spent on PBS. Conventional surveillance is usually restricted to a limited number of infections over a short period of time due to workload and time restraints. Data collection using COSARA is integrated in the clinical workflow, closely linked to decision support, and can be pursued on a prospective continuous basis without much additional effort.

Conflict of interest statement

None declared.

Funding source

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B. A COMPLETE AND MULTIFACETED OVERVIEW OF ANTIBIOTIC USE AND INFECTION DIAGNOSIS IN THE INTENSIVE CARE UNIT: RESULTS FROM A PROSPECTIVE FOUR-YEAR REGISTRATION

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Submitted

4.B.1 Abstract

Purpose:

The implementation of antibiotic stewardship programs requires detailed information on overall antibiotic use, prescription indication and ecology. However, longitudinal data of this kind are scarce. Computerization of the patient chart has offered the potential to collect complete data of high resolution. To gain insight in our global antibiotic use, we aimed to explore antibiotic prescription in our intensive care unit (ICU) from various angles over a prolonged time period.

Methods:

We studied all adult patients admitted to Ghent University Hospital ICU between January 1st 2013 until December 31st 2016. Antibiotic prescription data were prospectively merged with clinical diagnostic (e.g. infection focus, severity, probability at start) and microbiology data by ICU physicians during daily workflow through a dedicated software program. Appreciation of infection probability (high/moderate/low) was reassessed by dedicated ICU physicians during the treatment.

Results:

During the study period, 8763 patients were admitted with an overall antibiotic consumption of 1232 days of therapy (DOT)/1000 patient days. Of all DOT, 52.7% was used to treat infections with high probability; whereas prophylactic treatment accounted for 25%. Infections were microbiologically confirmed in 56% (3496/6206) of cases. Bacterial infections were mainly respiratory and abdominal (49% and 19% respectively). Of the total DOT used for respiratory infection, 42% was for moderate to low probability infections, whereas for abdominal infection, this was only 15%.

Conclusions:

We were able to construct a longitudinal, multifaceted dataset on global antibiotic use and infection diagnosis. Categorization of prescriptions by infection probability may guide construction and monitoring of future stewardship actions.

4.B.2 Introduction

Antibiotics are among the most often prescribed drugs in an intensive care unit (ICU).[2, 6] Whereas the positive impact of timely and appropriate antimicrobial therapy on outcome in severe bacterial infection is beyond discussion, the strong association between antibiotic exposure and the emergence of antibiotic-resistant bacteria mandates rationalization of antibiotic prescription. The concept of 'antibiotic stewardship' refers to policies and interventions to optimize antibiotic therapy and restrict unnecessary use.[1, 3, 23, 26, 27, 119, 120] The latter comprises avoiding antibiotic prescription for non-infectious disease, limiting use of broad-spectrum drugs when a narrower antimicrobial spectrum suffices and shortening duration of therapy when prolonged antibiotic courses do not provide benefit.[29, 35, 121]

Surveillance of antibiotic prescription is a first essential step to measure antibiotic expenditure, to document physician's incentives to prescribe antibiotics and to identify areas of potential overuse or misuse which could then be a target for antimicrobial stewardship interventions.[27, 28, 122, 123] In general, surveillance metrics are derived from antibiotic prescription data (pharmacy-based), microbiology results (laboratory-based) or diagnostic codes (administration-based) or a combination thereof. However, surveillance is not the primary purpose of these sources of information: they mostly have poor matching of antibiotic prescription with the corresponding clinical and microbiological data. This limits their ability to represent the complex nature of the antibiotic treatment decision-making process and thus their practical usefulness.[38, 45, 48] Prospective surveillance on the ICU floor is more precise and informative but since it is demanding in time and resources, it is usually only applied for relatively short periods of time or for a limited scope of prescription, e.g. for certain classes of reserved antibiotics.[52] The computerization of the patient ICU chart has offered the potential to record healthcare processes as complete data of high resolution in a way that minimally interferes with the healthcare-deliverer's workflow.[102]

In this manuscript, we present a complete and in-depth analysis of global antibiotic prescription and infection diagnosis in a university hospital ICU over a four-year period. These data were collected with the help of a locally developed software program which has been designed to link pharmaceutical, clinical and microbiological data together with diagnostic interpretation while performing daily bedside clinical work. As such, we tried to get a bird's eye view of our local antibiotic prescribing practices, which can then serve as a starting point for the future construction of an antibiotic stewardship program (ASP).

4.B.3 Materials and methods

Setting

This study was conducted from January 1st 2013 until December 31st 2016 at the medical (14 beds) and surgical (22 beds) ICU of Ghent University Hospital (1054 beds). The Ghent University Hospital Ethics Committee approved the study (registration number B670201628197) and waived informed consent based on the non-interventional nature of this study. Only patients aged 16 years or older were included.

An Intensive Care Information System (Centricity Critical Care, GE Health Care) integrating computerized physician order entry for medication prescriptions, computerized medication administration recording and clinical patient monitoring data is available bedside since 2003. Patients are managed in a closed ICU model and all antibiotic prescriptions are at the discretion of the attending senior ICU physician, without the use of stringent protocols or antibiotic restrictions. Empirical antibiotic choices are guided by systematically collected surveillance cultures whenever available. Turnaround time for microbial identification and antimicrobial susceptibility is 24-48 h for blood cultures and 48 h for other cultures. Direct microscopic examination is performed on all diagnostic respiratory and per-operative samples. Pathogen identification is routinely performed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). All microbiology results are reported electronically. Interdisciplinary staff meetings with medical microbiologists reviewing all antibiotic prescriptions take place once weekly in the medical ICU and three times weekly in the surgical ICU; these staffs also include the presence of infectious diseases specialists in the surgical ICU. In addition, daily advice and follow-up by these specialties is possible on a demand basis for individual cases. Treatment duration and opportunities for antibiotic de-escalation are evaluated daily by the attending ICU physician and during the interdisciplinary discussions.

A software program with the acronym COSARA (Computer-based Surveillance and Alerting of infections, antimicrobial Resistance and Antibiotic consumption in the ICU) was developed by a consortium of the Ghent University Hospital ICU department and the Department of Information Technology (INTEC) of the Faculty of Engineering of Ghent University.[102] The project was funded by the Flemish government. The goal of COSARA is to support the ICU physician in the daily workflow by automatically integrating all relevant infection-related data (clinical parameters, antibiotic prescription, laboratory variables including microbiology and chest X-ray images) from different data sources and presenting these as a graphic overview. The antibiotic prescription is graphically presented as a horizontal bar, running along a timeline and lengthening upon duration of this prescription (antibiotic bar). This bar is accompanied by a second bar running in parallel and describing the indication for this antibiotic (infection bar).

The infection bar is created in a two-step fashion. A preliminary version is fed by data from a short questionnaire that 'pops up' in real-time after any antibiotic prescription and inquires the prescriber about indication, likely focus, severity and probability of infection and presence of microbiological data guiding the antibiotic choice. This preliminary bar can be altered manually when more data concerning the origin and clinical evolution of the infection become available. Multiple antibiotic prescriptions can thus be linked with the same infection bar; in addition, the same antibiotic bar can be linked with multiple infection bars (e.g. antibiotic prescribed for simultaneous intra-abdominal and respiratory infection). For each infectious episode, focus, severity and probability of infection is selected from a drop-down menu. Probability is classified as low, moderate or high, as described previously,[124] using clinical, radiological and microbiological criteria. An infection was defined as ICU-acquired if it occurred 48 h or more after admission to the ICU. The coupled antibiotic-infection bars can be linked to microbiological culture results; microbial pathogens may be designated as causative pathogens, or as non-causative pathogens influencing antibiotic prescription (e.g. nasal carriage of methicillin-resistant *Staphylococcus aureus* promoting glycopeptide prescription in suspected pneumonia with negative sputum cultures). For this study, all preliminary infection bars were reviewed, completed or modified if necessary by the investigators LDB and PD after consultation of the treating ICU physician or the patient charts.

Antimicrobial days of therapy (DOT) per admission and per patient days is recommended as utilization metric by the STEWARDS panel and others.[122, 123, 125] In agreement with the recommendations of the Centers for Disease Control and Prevention - National Healthcare Safety Network (CDC-NHSN), DOT is defined as the number of days with systemic administration of at least one dose of an antimicrobial agent as recorded by COSARA.[35]

Statistics

Categorical variables were expressed as frequencies (percentages), continuous variables were described as median values with the interquartile range (IQR; 25–75th percentile). Statistical analysis was performed using R Statistical Software (version 3.4.2).

4.B.4 Results

Patients

A total of 10743 ICU admissions were recorded in 8763 patients resulting in a total of 47403 patient days from January 1st 2013 until December 31st 2016. ICU and hospital mortality was 10.7% (n=936) and 15% (n=1314) respectively. Median APACHE II score at admission was 18 (IQR 13-25). Mechanical ventilation was provided in 3958 admissions (36.8%) with a median duration of 2 days (IQR 1-6), resulting in 20897 ventilation days. Vasopressor therapy was administered in 3639 admissions (33.9%) with a median duration of 2 days (IQR 2-4).

Methicillin resistance was present in 23% of the *Staphylococcus aureus* isolates in our ICU population. Vancomycin resistance was present in 1.9% of the *Enterococcus* species isolates. Extended spectrum beta-lactamase production (ESBL) was present in 33% of *Enterobacteriaceae* isolates, whereas carbapenemase production was present in 1.2%.

Patients were exposed to at least one antibiotic class in 66% of ICU admissions. An infection was present within the first 48 h of ICU admission in 35% (3804/10743) of admissions. An ICU-acquired infection was diagnosed in 23% (1096/4851) of admissions with an ICU length of stay of more than 48 h. Detailed information on antibiotic exposure and infection diagnosis per ICU episode is provided in table 5.

Table 5: Antibiotic exposure and infection diagnosis per ICU episode

	LOS ICU <48h (n=5892)	LOS ICU ≥ 48h (n=4851)
Antibiotic exposure (%)		
n antibiotic classes		
0 classes	2892 (49%)	800 (16%)
1 class	2309 (39%)	1489 (31%)
2 classes	519 (9%)	1050 (22%)
3 classes	127 (2%)	655 (14%)
> 3 classes	45 (1%)	857 (18%)
Carbapenem exposure		
2013-2016	142 (2%)	679 (14%)
2013	34/1439 (2%)	200/1149 (17%)
2014	54/1519 (4%)	169/1228 (14%)
2015	20/1447 (1%)	148/1265 (12%)
2016	34/1487 (2%)	162/1209 (13%)
Fluoroquinolone exposure		
2013-2016	205 (3%)	997 (21%)
2013	52/1439 (4%)	261/1149 (23%)
2014	48/1519 (3%)	270/1228 (22%)
2015	57/1447 (4%)	218/1265 (17%)
2016	48/1487 (3%)	248/1209 (21%)
Glycopeptides exposure		
2013-2016	141 (2%)	551 (11%)
2013	37/1439 (3%)	136/1149 (12%)
2014	40/1519 (3%)	150/1228 (12%)
2015	38/1447 (3%)	139/1265 (11%)
2016	26/1487 (2%)	126/1209 (10%)
Linezolid exposure		
2013-2016	37 (1%)	292 (6%)
2013	12/1439 (1%)	66/1149 (6%)
2014	12/1519 (1%)	76/1228 (6%)
2015	5/1447 (0.3%)	67/1265 (5%)
2016	8/1487 (0.5%)	83/1209 (7%)
Infection diagnosis (%)		
Infection within the first 48h of ICU admission	1182 (20%)	2622 (54%)
ICU-acquired infection (≥ 48h)		
1 infection	-	706 (15%)
2 infections	-	239 (5%)
> 2 infections	-	151 (3%)

LOS = length of stay, ICU = intensive care unit

Prescription indication

A total number of 10731 treatment courses (infection bars) was recorded during the study period. Respectively 4525 (42.2%) and 6206 (57.8%) of these courses were prescribed for prophylaxis or for infection. Fungal infections represented 8% (520/6206) of the infectious episodes. Infections were microbiologically confirmed in 56% (3169/5686) and 63% (327/520) of bacterial and fungal infections, respectively. Infections were ICU-acquired in 28% of cases (1767/6206). The focus of the bacterial infections was predominantly respiratory and abdominal (respectively, 49% and 19%). Infection probability was classified as high, moderate or low in respectively 50%, 34% and 16% of the respiratory infections compared to respectively 76%, 16% and 8% of the abdominal infections. Only 19% of the respiratory infections were classified as ventilator-associated. A total of 345 ventilator-associated pneumonia (VAP) and 182 ventilator-associated tracheobronchitis (VAT) were diagnosed, resulting in VAP and VAT incidences of 16.5/1000 ventilation days and 8.7/1000 ventilation days, respectively. The median treatment duration of VAP and VAT episodes on the ICU was respectively, 7 days [IQR 5-9] and 6 days [IQR 4-7]. See figure 9 for more details on bacterial and fungal infection focus. See table 6 for more detailed information on the duration of therapy per focus of infection.

Antimicrobial utilization

A total of 14908 antibiotic courses (antibiotic bars) were administered, resulting in 58413 DOT (1232 DOT/1000 patient days). Detailed utilization analysis per antibiotic agent and infection probability is presented in table 7a. Utilization analysis per antibiotic agent over the study years 2013-2016 is presented in table 7b. Anti-pseudomonal penicillins combined with a beta-lactamase inhibitor, non-anti-pseudomonal penicillins combined with a beta-lactamase inhibitor and fluoroquinolones were the most frequently consumed antibiotic classes (respectively, 218 DOT/1000 patient days, 172 DOT/1000 patient days and 114 DOT/1000 patient days), azoles were the predominantly used antifungal class (162 DOT/1000 patient days).

Only 36% of the total antifungal DOT was used to treat infections with a high probability, whereas this figure was 56% of the total DOT in the case of antibacterial agents. First generation cephalosporins, folate pathway inhibitors and monobactams were predominantly used in the prophylactic setting. However, even 32% of the total DOT of non-antipseudomonal penicillins combined with a beta-lactamase inhibitor were prescribed prophylactically. Indications for prophylactic therapy in the non-antipseudomonal penicillins combined with a beta-lactamase inhibitor group were mainly aspiration (30%), severe trauma (30%), perioperative prophylaxis (20%) and variceal bleeding (6%).

Respectively, 36% and 21% of the total antibacterial DOT was used to treat respiratory and abdominal infections. Of the total amount of DOT used to treat bacterial respiratory infections, 42% was used to treat infections with a moderate and low probability, compared to 15% of the DOT used for bacterial abdominal infections.

Microbiology

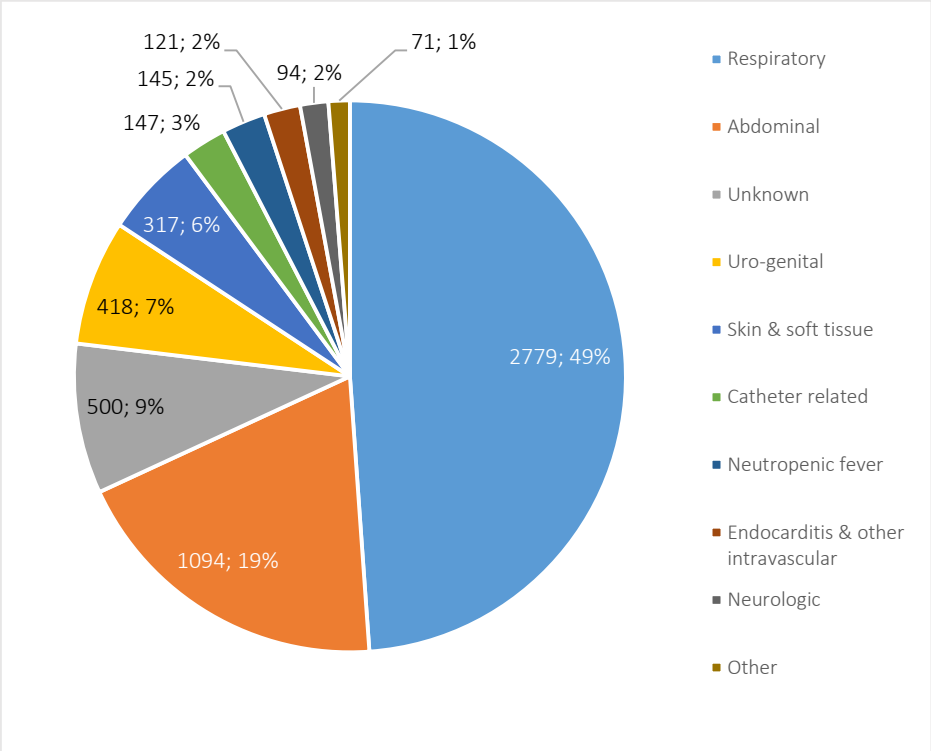
Enterobacteriaceae were the predominant bacterial species that were designated as causative pathogens in both respiratory and abdominal infections (respectively, 39% and 46% of all pathogens linked to these groups of infections). Amoxicillin/clavulanic acid resistance and cefuroxime resistance was present in 48% and 39%, respectively. *Enterococci* were the second most prevalent pathogens that were linked as causative in the abdominal infections and ampicillin resistance was present in 44% of the isolates (figure 10).

Table 6: Duration of therapy per focus of infection

Focus of infection	All antibiotic courses		Antibiotic course completed on ICU	
	Number of infections	Duration of therapy days (median, [IQR])	Number of infections	Duration of therapy days (median, [IQR])
Respiratory infection	2779	5 [3-7]	1389	6 [4-9]
Community-acquired pneumonia	281	4 [2-6]	123	6 [3.5-8]
Aspiration pneumonia	554	5 [3-8]	293	7 [5-9]
Hospital-acquired pneumonia	668	5 [3-7]	279	6 [4-8]
Healthcare-associated pneumonia	224	4 [2-6]	81	6 [4-8]
Tracheobronchitis (not ventilated)	174	4 [2-6]	83	5 [3-7]
Ventilation-associated pneumonia	345	7 [5-9]	264	7 [5-10]
Tracheobronchitis (ventilated)	182	6 [4-7]	134	6 [4-8]
Abdominal infection	1094	4 [2-8]	329	8 [4-14]
Intra-abdominal collection – abcedation	201	6 [3-12]	54	14.5 [7-20]
Localized secondary peritonitis	155	4 [2-9]	37	10 [7-15]
Diffuse secondary peritonitis	137	5 [3-10]	40	11.5 [7-18]
Uro-genital infection	418	3 [2-4]	158	3 [1-6]
Skin & soft tissue infection	317	4 [2-7]	82	7 [3-11]
Catheter related infection	147	4 [2-7]	66	5 [3-9]
Neutropenic fever	145	4 [2-7]	42	8 [3-9]

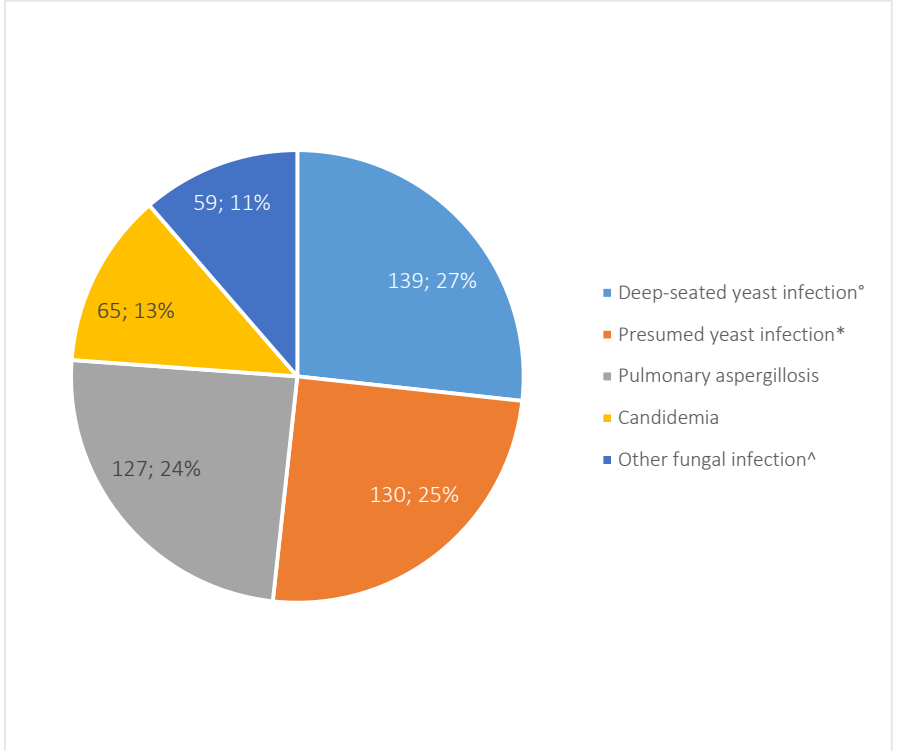
IQR = interquartile range (25^{th} -75^{th} percentile)

Figure 9: a) Focus of bacterial infections (n=5686)



Infection probability was classified as low, moderate or high in respectively 14%, 27% and 59% of the bacterial infections.

Figure 9: b) Focus of fungal infections (n=520)



Infection probability was classified as low, moderate or high in respectively 12%, 17% and 71% of the fungal infections.

° presence of yeast in a normally sterile body site combined with clinical signs of infection

* fungal infection considered clinically likely by treating physician in the absence of yeast in a normally sterile body site

^ mucocutaneous candidiasis, candidiasis of the genitourinary tract, extra-pulmonary *Aspergillus* infection, invasive non-*Aspergillus* mold infection

Figure 9: c) Bacterial respiratory infection (n=2779)

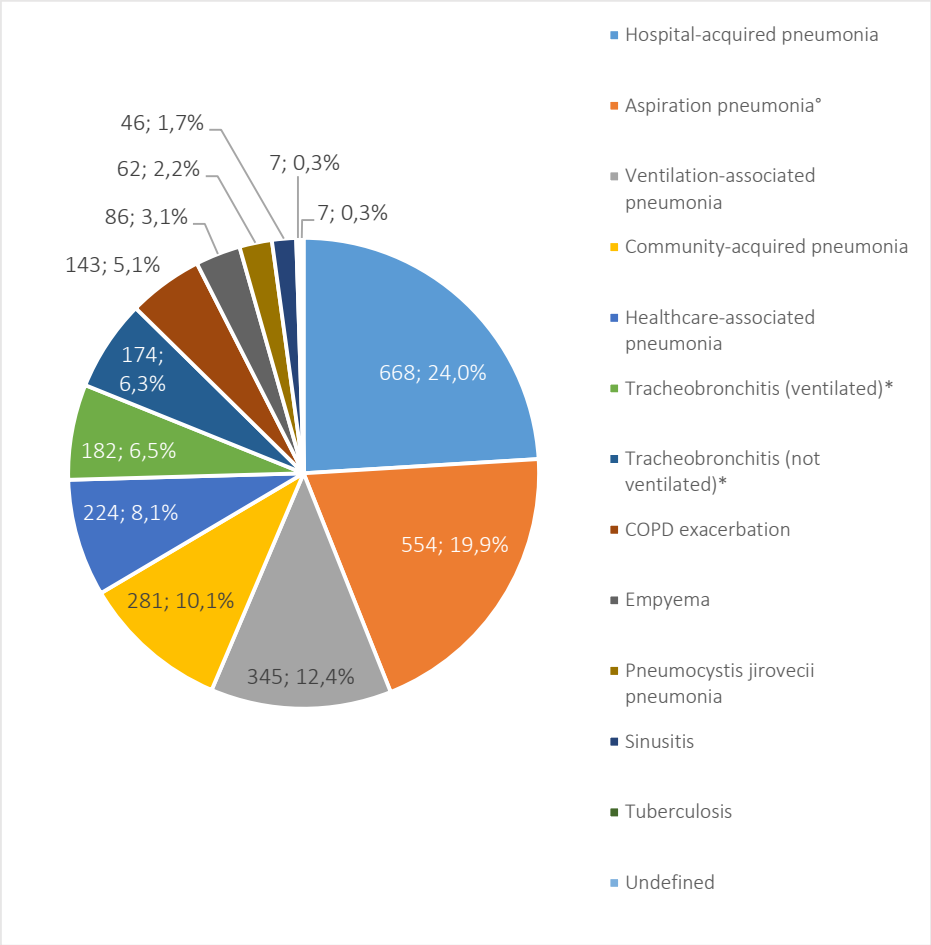
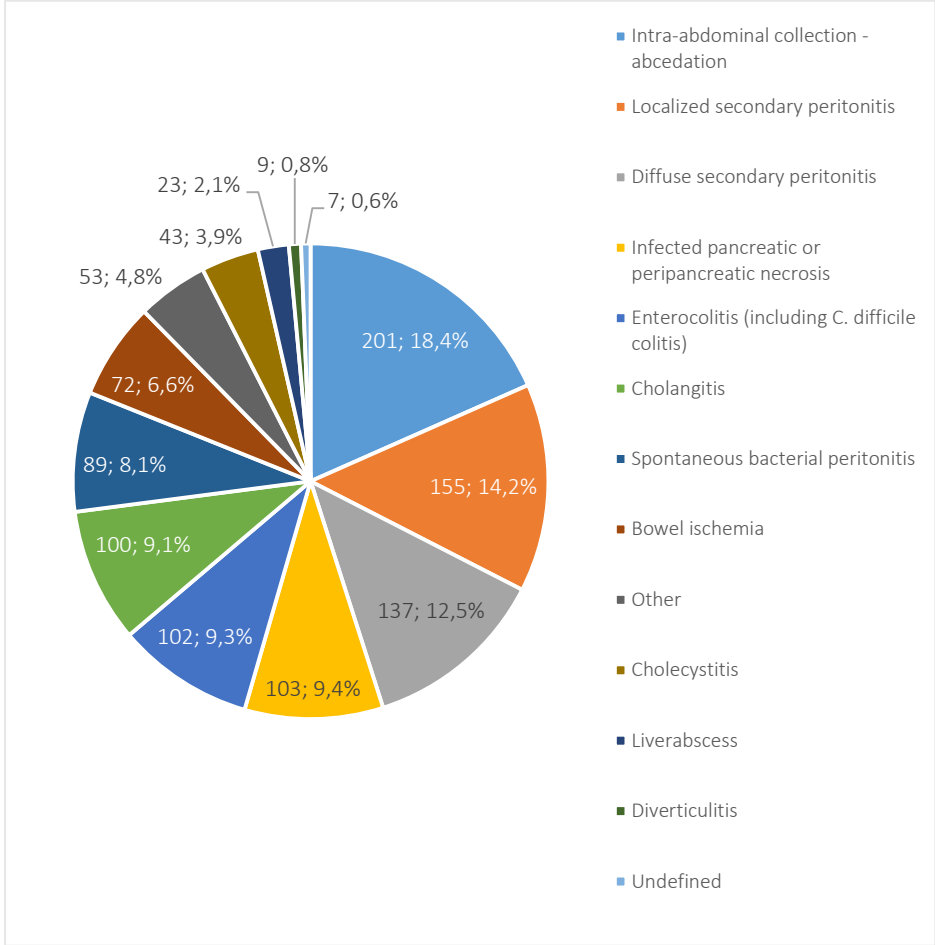


Figure 9: d) Bacterial abdominal infection (n=1094)



° bacterial pneumonia following macroaspiration

* tracheobronchitis criteria include: fever, purulent tracheobronchial secretions, isolation of a respiratory pathogen of a good quality lower respiratory tract sample, no radiographic signs of new pneumonia

Table 7a: Antimicrobial utilization per antimicrobial class and per infection probability

	DOT (%)	DOT/1000 patient days	DOT (% of total DOT/antibiotic class)			
			Infection present			Prophylactic treatment
			High probability	Moderate probability	Low probability	
Antibacterial class						
Aminoglycosides	474 (1.0)	10.0	388 (81.8)	67 (14.1)	5 (1.1)	6 (1.3)
Ansamycins	268 (0.5)	5.7	230 (85.8)	9 (3.4)	13 (4.9)	15 (5.6)
Carbapenems	4488 (9.1)	94.7	3438 (76.6)	697 (15.5)	221 (4.9)	110 (2.5)
1st gen. cephalosporins	2939 (6.0)	62.0	-	-	-	2939 (100)
2nd gen. cephalosporins	1192 (2.4)	25.1	398 (33.4)	324 (27.2)	169 (14.2)	301 (25.3)
3rd gen. cephalosporins	1955 (4.0)	41.2	1343 (68.7)	400 (20.5)	143 (7.3)	63 (3.2)
Fluoroquinolones	5385 (11)	113.6	3268 (60.7)	1285 (23.9)	367 (6.8)	448 (8.3)
Folate pathway inhibitor	3105 (6.3)	65.5	896 (28.9)	319 (10.3)	142 (4.6)	1747 (56.3)
Glycopeptides	2966 (6.0)	62.6	2163 (72.9)	438 (14.8)	172 (5.8)	169 (5.7)
Glycylcyclines	319 (0.6)	6.7	242 (75.9)	63 (19.7)	11 (3.4)	2 (0.6)
Lincosamides	806 (1.6)	17.0	564 (70.0)	140 (17.4)	42 (5.2)	60 (7.4)
Macrolides	1421 (2.9)	30.0	834 (58.7)	215 (15.1)	84 (5.9)	284 (20.0)
Monobactams	150 (0.3)	3.2	33 (22.0)	28 (18.7)	10 (6.7)	79 (52.7)
Nitrofurans	59 (0.1)	1.2	19 (32.2)	16 (27.1)	7 (11.9)	17 (28.8)
Nitroimidazoles	1289 (2.6)	27.2	976 (75.7)	147 (11.4)	61 (4.7)	92 (7.1)
Oxazolidinones	1780 (3.6)	37.6	1434 (80.6)	212 (11.9)	53 (3.0)	69 (3.9)
Penicillins	1504 (3.1)	31.7	1212 (80.6)	188 (12.5)	86 (5.7)	15 (1.0)
Penicillins + beta-lactamase inhibitor	8136 (16.5)	171.6	3267 (40.2)	1605 (19.7)	660 (8.1)	2588 (31.8)
Anti-pseudomonal penicillins + beta-lactamase inhibitor	10342 (21.0)	218.2	6405 (61.9)	2292 (22.2)	808 (7.8)	800 (7.7)
Phosphonic acids	27 (0.1)	0.6	3 (11.1)	17 (63.0)	6 (22.2)	1 (3.7)
Polymyxins	469 (1.0)	9.9	311 (66.3)	97 (20.7)	19 (4.1)	42 (9.0)
Tetracyclines	95 (0.2)	2.0	82 (86.3)	1 (1.1)	1 (1.1)	11 (11.6)
Total antibacterial	49169 (100)	1037.3	27506 (55.9)	8560 (17.4)	3080 (6.3)	9858 (20.0)
Antifungal class						
Azoles	7684 (83.1)	162.1	2123 (27.6)	415 (5.4)	222 (2.9)	4809 (62.6)
Echinocandins	1354 (14.6)	28.6	1022 (75.5)	176 (13.0)	93 (6.9)	56 (4.1)
Polyenes	206 (2.2)	4.3	138 (67.0)	37 (18.0)	29 (14.1)	-
Total antifungal	9244 (100)	195.0	3283 (35.5)	628 (6.8)	344 (3.7)	4865 (52.6)
TOTAL	**58413 (100)**	**1232.3**	**30789 (52.7)**	**9188 (15.7)**	**3424 (5.9)**	**14723 (25.2)**

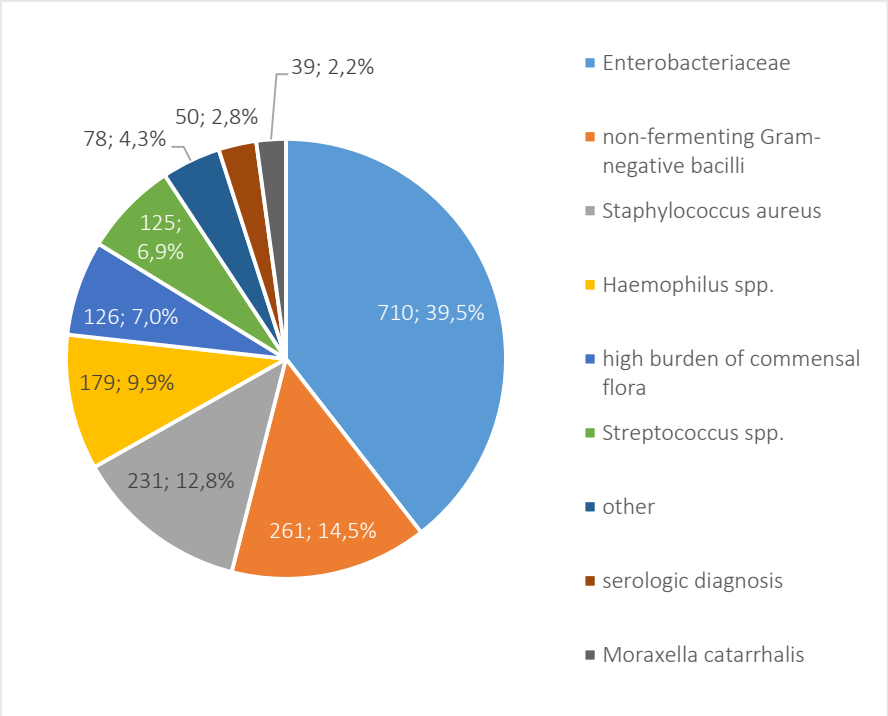
DOT, days of therapy

Table 7b: Antimicrobial utilization per antimicrobial class and per year

		DOT/1000 patient days				
	DOT (%)	2013-2016	2013	2014	2015	2016
Antibacterial class						
Aminoglycosides	474 (1.0)	10.0	8.0	13.0	8.6	10.4
Ansamycins	268 (0.5)	5.7	6.0	6.4	6.7	3.6
Carbapenems	4488 (9.1)	94.7	102.6	90.0	90.8	95.0
1st gen. cephalosporins	2939 (6.0)	62.0	56.8	63.5	61.1	66.8
2nd gen. cephalosporins	1192 (2.4)	25.1	36.0	28.8	20.2	15.1
3rd gen. cephalosporins	1955 (4.0)	41.2	41.0	37.0	39.5	47.4
Fluoroquinolones	5385 (11)	113.6	116.9	120.5	94.8	121.5
Folate pathway inhibitor	3105 (6.3)	65.5	76.8	68.4	55.9	60.2
Glycopeptides	2966 (6.0)	62.6	66.8	61.1	67.1	55.3
Glycylcyclines	319 (0.6)	6.7	6.7	4.2	7.2	8.9
Lincosamides	806 (1.6)	17.0	17.3	15.2	15.2	20.3
Macrolides	1421 (2.9)	30.0	18.2	29.7	37.0	35.5
Monobactams	150 (0.3)	3.2	3.1	3.5	3.9	2.1
Nitrofurans	59 (0.1)	1.2	1.7	1.4	1.0	0.8
Nitroimidazoles	1289 (2.6)	27.2	26.9	26.3	28.4	27.1
Oxazolidinones	1780 (3.6)	37.6	32.6	38.6	35.5	43.6
Penicillins	1504 (3.1)	31.7	33.0	26.0	24.2	43.6
Non-anti-pseudomonal penicillins + beta-lactamase inhibitor	8136 (16.5)	171.6	176.3	161.7	179.4	169.4
Anti-pseudomonal penicillins + beta-lactamase inhibitor	10342 (21.0)	218.2	215.8	219.3	220.5	217.2
Phosphonic acids	27 (0.1)	0.6	-	-	0.9	1.4
Polymyxins	469 (1.0)	9.9	12.1	14.3	7.0	5.9
Tetracyclines	95 (0.2)	2.0	-	0.7	7.5	-
Total antibacterial	49169 (100)	1037.3	1054.8	1029.6	1012.5	1051.2
Antifungal class						
Azoles	7684 (83.1)	162.1	151.2	176.4	159.2	161.7
Echinocandins	1354 (14.6)	28.6	29.3	19.2	35.7	30.3
Polyenes	206 (2.2)	4.3	3.3	6.3	3.3	4.5
Total antifungal	9244 (100)	195.0	183.8	201.9	198.2	196.5
TOTAL	**58413 (100)**	**1232.3**	**1238.6**	**1231.4**	**1210.7**	**1247.7**

DOT, days of therapy

Figure 10a) Pathogens linked to bacterial respiratory infection(n=1828)



Enterobacteriaceae = *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli, Hafnia* spp., *Klebsiella* spp., *Morganella* spp.., *Proteus* spp., *Providencia* spp., *Serratia* spp.

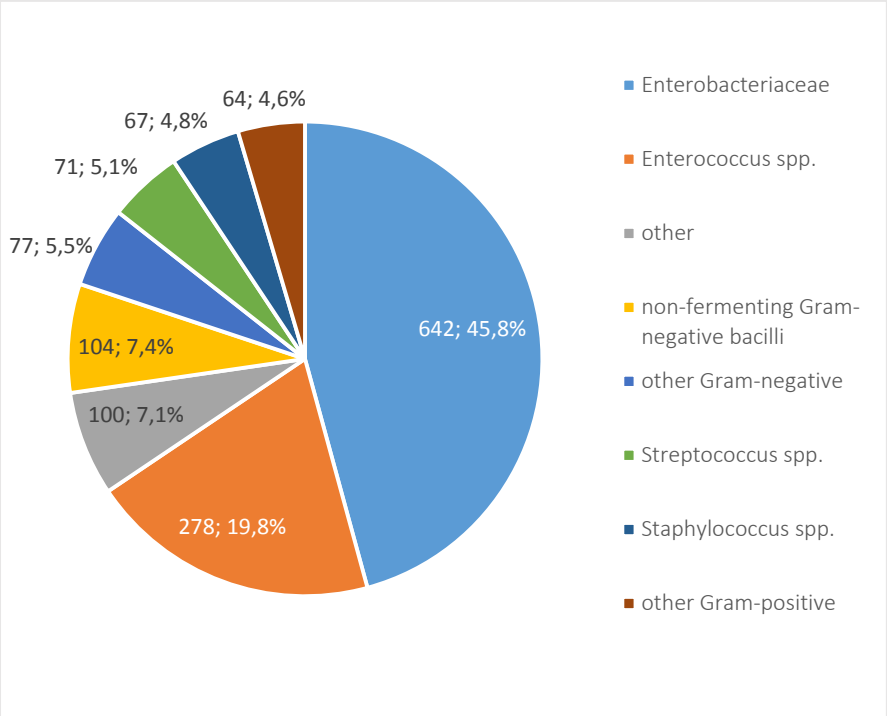
Non-fermenting Gram-negative bacilli = *Achromobacter* spp., *Acinetobacter* spp., *Stenotrophomonas* spp., *Pseudomonas* spp., other non-fermenting Gram-negative bacilli

Streptococcus spp.= *Streptococcus pneumoniae, Streptococcus pyogenes*, Viridans streptococci, other streptococci

Other = culture results of referral hospital

Serologic diagnosis = *Legionella pneumophila* antigen, *Streptococcus pneumoniae* antigen

Figure 10b) Pathogens linked to bacterial abdominal infection (n=1403)



Enterobacteriaceae = *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli, Hafnia* spp., *Klebsiella* spp., *Morganella* spp., *Proteus* spp., *Providencia* spp., *Salmonella* spp., *Serratia* spp., *Yersinia* spp.

Enterococcus spp. = *Enterococcus faecalis, Enterococcus faecium*, other enterococci

Other = culture results of referral hospital

Non-fermenting Gram-negative bacilli = *Achromobacter* spp., *Stenotrophomonas* spp., *Pseudomonas* spp., other non-fermenting Gram-negative bacilli

Streptococcus spp.= *Streptococcus pneumonia*, Viridans streptococci, other streptococci

Staphylococcus spp. = *Staphylococcus aureus*, coagulase-negative staphylococci, other

Other Gram-negative = e.g. *Bacteroides* spp., *Prevotella* spp., *Aeromonas* spp., *Campylobacter* spp.

Other Gram-positives = e.g. *Clostridium* spp., *Bacillus* spp.

4.B.5 Discussion

In this manuscript, we demonstrate the versatility of a detailed database on antibiotic use and infection diagnosis which is prospectively built by linking prescription, clinical and microbiological data of individual ICU patients during clinical workflow. This allows various analyses which respectively center on patient admissions, prescription indication and infection diagnosis, antibiotic utilization and microbiology and as such may be useful to support various aspects of hospital infection control and antibiotic stewardship. To the best of our knowledge, our study is the largest single center study providing epidemiological data on antibiotic consumption and infections treated in the ICU in terms of number of ICU beds (36) and time (4 years).

Our study confirms that the antibiotic burden is very high, with exposure to at least one antibiotic class in 66% of all admitted patients and 84% of patients with an ICU stay of more than 48 h, respectively. These figures are consistent with the results of the one-year prospective surveillance study of Bergmans et al. and with the EPIC II point prevalence study.[2, 6]

The need for detailed antibiotic prescription surveillance and feedback to the clinician was already acknowledged in the very early stages of antimicrobial stewardship, but up until now literature is riddled with discussion about which appropriate measures to select.[25, 27, 122, 123, 126] In 2016, the consensus results of an expert panel on metrics assessing the impact of stewardship interventions on a patient-level in an acute-care setting were published.[122] Potential metrics were evaluated for four distinct criteria, one of them being the feasibility to monitor the metric in any hospital with an electronic health record. Only six metrics were retained by the expert panel as suitable for ready implementation: incidence of healthcare-facility and hospital-onset *Clostridium difficile* infection, rates of antibiotic-resistant pathogens, days of antibiotic therapy/number of admissions, days of antibiotic therapy/patient days, and redundant therapy events. All of these metrics may be derived from separate electronic data sources (clinical, pharmacy, microbiology) and a connection between the different elements is not mandatory; however, these metrics are quite crude and unable to provide insight in antibiotic prescription. By linking these sources a deeper understanding of the different factors driving antimicrobial use in the ICU can be obtained, as illustrated by this study.

For example, the respiratory system accounts for half of identified sources of infection and more than one third of the total antibacterial DOT. Compared to the abdominal infections, which represent the second largest group of infections and destination for antibiotic consumption, respiratory infections were less frequently categorized as highly probable (75% versus 50% respectively), which also reflected in the amount of DOT that was designated to treat these

highly probable infections (85% of the total DOT of abdominal and 56% of the total DOT of respiratory infections). One quarter of the infections that is diagnosed in our ICU is ICU-acquired, which is in contrast with the study of Bergmans et al. where half of the infections were ICU-acquired and almost exclusively occurred in ventilated patient. Whereas the authors of the previous study concluded that stewardship should be focused on the prevention of ventilator-associated respiratory infections, this statement may less apply to our ICU population. In addition, restricting duration of antibiotic therapy in VAP of high probability will offer little gain, as the median treatment duration was only 7 days. In contrast, a more restrictive use of antibiotics in suspected respiratory tract infections with cultures remaining negative and/or a swift clinical resolution, could result in a more profound reduction of antibiotic consumption. In addition, we observed that prophylactic treatment accounted for one fourth of the total DOT. Although duration of prophylactic treatment is still a matter of debate for some conditions, clear guidelines and new study results recommending on indication and duration have become available over the last years.[127-131] We believe that introduction of guidelines on non-perioperative prophylaxis, which are currently unavailable in our hospital and ICU, could lead to a reduction in antibiotic use.

Despite the recognition of the importance of high-quality surveillance data to support antibiotic stewardship, few studies have provided detailed data of ICU global antibiotic consumption and infection diagnosis over an extended period of time.[6, 52, 132] This may reflect the difficulties in continuous prospective merging of infection related data due to personnel and time restraints. In fact, while the authors of the study of Bergmans et al. felt that their proposed surveillance model in which they categorize antibiotic indications as either prophylaxis, bacteriologically proven or non-bacteriologically proven (clinical suspicion), would be suitable for a more widespread use, few publications offering a similarly wide scope on antibiotic use in the ICU have followed since.[6] In our ICU, the COSARA software platform facilitated the integration of antibiotic, clinical and microbiological information during the workflow of daily bedside clinical rounds and weekly multidisciplinary staff meetings, hereby illustrating that sustained prospective detailed surveillance is an achievable ambition with the help of information technology.[102, 124] The sustainability of this surveillance is probably to a certain extent due to the rather intuitive approach of labeling infections by the physician choosing from a drop-down menu of possible diagnoses and categorization by infection probability. While the result closely reflects physician's judgment and attitude in daily practice, it does not formally adhere to criteria such as provided by the CDC or Hospitals in Europe Link for Infection Control through Surveillance (HELICS). A previous analysis assessing the validity of the diagnostic information recorded as such in COSARA compared to conventional surveillance data gathered by using checklists based on CDC-NHSN criteria showed good agreement between both surveillance

methods.[124] However, a lack of precision may hamper comparisons between centers (as required for benchmarking) and over time (changing perception). This may to a certain extent be remedied by filtering sets of infection labels for the fulfillment of objective criteria as e.g. presence of positive microbiological cultures, biochemical findings exceeding a given threshold and noting of clinical signs in a computerized medical file.

Our study has limitations. First, building up the database starting from computerized physician order entry depends on adequate filling in of the 'pop-up' questions that are triggered by it, and by the persistent commitment of attending physicians or infection control personnel in linking the various information sources and finalizing infection diagnosis. Second, as stated before, the lack of adhering to strict criteria in labeling infection diagnosis in the current design hampers multicenter application.[124] Probably a trade-off has to be found between practical feasibility of continued infection registration at one hand, and precision in diagnosis at the other. In addition, while COSARA software is compatible with various Intensive Care Information Systems, it has not been formally tested whether our surveillance is applicable over differing ICU settings and staffing structures. Third, it remains to be tested to what extent high-quality surveillance may translate in effective stewardship intervening with treatment decisions of the attending ICU physician.

Conclusions

We were able to get a bird's eye view on global antibiotic use and infection diagnosis in our ICU over a 4-year time period by analysis of a multifaceted dataset which was collected during the daily clinical workflow of ICU physicians with the help of information technology. Grouping of prescriptions by infection probability may assist in planning and monitoring of future stewardship actions.

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Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

C. DEVELOPMENT OF ANTIBIOTIC TREATMENT ALGORITHMS BASED ON LOCAL ECOLOGY AND RESPIRATORY SURVEILLANCE CULTURES TO RESTRICT THE USE OF BROAD-SPECTRUM ANTIMICROBIAL DRUGS IN THE TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA IN THE INTENSIVE CARE UNIT: A RETROSPECTIVE ANALYSIS

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4.C.1 Abstract

Introduction:

Timely administration of appropriate antibiotic therapy has been shown to improve outcome in hospital-acquired pneumonia (HAP). Empirical treatment guidelines tailored to local ecology have been advocated in antibiotic stewardship programs. We compared a local ecology based algorithm (LEBA) to a surveillance culture based algorithm (SCBA) in terms of appropriate coverage and spectrum of antimicrobial activity.

Methods:

We retrospectively assessed 2 hypothetical empirical antibiotic treatment algorithms for HAP on an existing high-quality prospectively collected database in a mixed 36-bed tertiary intensive care unit (ICU). Data on consecutive episodes of microbiologically confirmed HAP were collected over a period of 40 months and divided in a derivation (1 July 2009 to 31 October 2010) and validation (1 November 2010 until 31 October 2012) cohort. On the derivation cohort we constructed a LEBA, based on overall observed bacterial resistance patterns, and a SCBA, which targeted therapy to surveillance culture (SC) in the individual patient. Therapy was directed against pathogens found in respiratory SC collected two to five days before HAP, and in the absence of these, presence or absence of multidrug-resistant (MDR) pathogens in other SC dictated broad-spectrum, respectively narrow-spectrum antibiotic therapy. Subsequently, LEBA and SCBA were retrospectively reviewed and compared with actually prescribed antibiotics in the validation cohort.

Results:

The first 100 HAP episodes made up the derivation cohort and the subsequent 113 HAP episodes the validation cohort. Appropriate antibiotic coverage rates by applying LEBA and SCBA were 88.5% and 87.6%, respectively, and did not differ significantly with respect to appropriateness of the actually prescribed initial therapy (84.1%). SCBA proposed more narrow spectrum therapy as compared to LEBA and the actually prescribed antimicrobials (P <0.001). SCBA recommended significantly less combination therapy and carbapenems compared to LEBA (P <0.001). SCBA targeted antibiotics to recent respiratory SC in 38.1% (43 out of 113 episodes) of HAP; in these cases adequacy was 93% (40 out of 43).

Conclusion:

Rates of appropriate antimicrobial coverage were identical in LEBA and SCBA. However, in this setting of moderate MDR prevalence, the use of SCBA would result in a significant reduction of the use of broad-spectrum drugs and may be a preferential strategy when implementing antibiotic stewardship programs.

4.C.2 Introduction

Antibiotic stewardship refers to efforts both made to improve appropriateness of antibiotic prescription and to reduce antibiotic selection pressure by limiting unnecessary use of antibiotics, especially those with a broad spectrum.[26, 133] As hospital-acquired pneumonia (HAP) is a frequent indication for antibiotic prescription as well as a manifestation of antibiotic resistance, antibiotic policy for HAP is an important target area for antibiotic stewardship. Early appropriate antibiotic therapy is a major determinant of outcome in HAP: early refers usually to the time of the initial clinical diagnosis or suspicion of pneumonia.[11, 80, 134] As at this early stage, microbial etiology is still unknown and potentially multidrug-resistant (MDR), broad-spectrum antibiotics, often in combination schemes, are advocated as empirical therapy. As the microbial and resistance patterns are variable across ICUs, these empirical schemes have to be matched to the local situation in order to achieve high rates of appropriate coverage whilst avoiding unnecessary broad-spectrum antibiotics.[135, 136] In addition, algorithms may contribute to antibiotic stewardship as they assist to rationalize antibiotic choices and reduce prescription variability, improve overall appropriateness and restrain use of certain drug classes such as carbapenems. As a more controversial approach, early antibiotic therapy may be guided by surveillance cultures (SC) to improve its appropriateness.[87, 137-139] With this approach, antibiotics are essentially selected in order to cover colonizing pathogens in the individual patient.

In this study, we developed two algorithms for initial antibiotic prescription in ICU patients with suspected HAP. We aimed a) to assess the potential of an algorithm to aid in antibiotic stewardship in our setting and b) quantify the contribution of SC to antibiotic stewardship as compared to empirical therapy based upon local epidemiology.

4.C.3 Materials and methods

Clinical setting and design

This retrospective analysis was conducted at the 14-bed Medical ICU and the 22-bed Surgical ICU of the Ghent University Hospital (1,056 beds). With the aid of the software application, Computer-based Surveillance and Alerting of infections, Antimicrobial Resistance and Antibiotic consumption in the ICU (COSARA), all episodes of pneumonia were registered prospectively from 1 July 2009 to 31 October 2012. COSARA assists the attending ICU-physician in acquiring an overview of the various daily collected data related to infection diagnosis (trends in laboratory values, temperature, oxygenation et cetera) and treatment. This includes a graphical display of current and past antibiotic treatments as a timeline and provides direct links to a real-time copy of the various source records. The graphical interface allows the user to label infectious episodes during daily clinical rounds and interdisciplinary staff meetings to a predefined list of diagnoses in all patients admitted to the ICU. As such, the program facilitates the build-up of an extensive data-warehouse on antibiotic use and infection in the ICU.[102] During the study period treating physicians were not guided in the choice of the empirical antimicrobial by treatment algorithms. The Ghent University Hospital ethics committee approved the study and waived informed consent as prospective registration did not affect treatment decisions, and all subsequent analyses were performed retrospectively on an anonymized database. Only patients aged 16 years or above were included.

Definition of hospital-acquired pneumonia

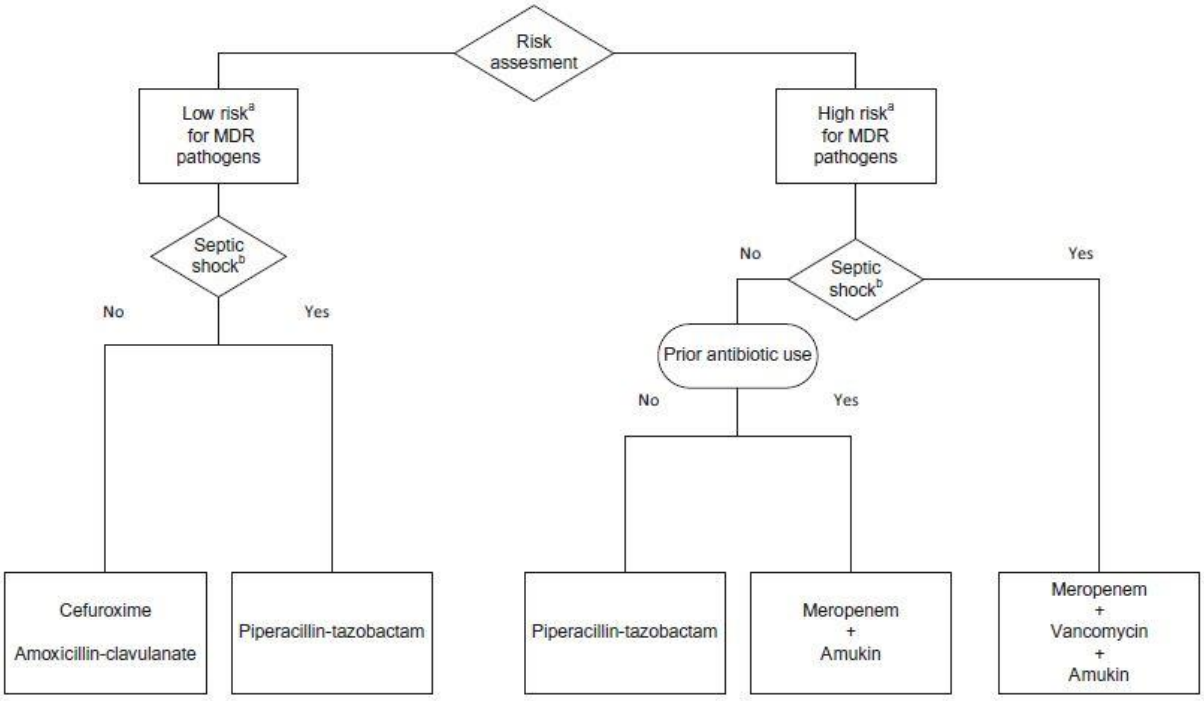
Pneumonia was defined to be hospital-acquired if it occurred 48 h or more after admission to the hospital. HAP was defined clinically as the presence of new and/or progressive and persistent pulmonary infiltrates on the chest radiograph, in combination with two or more of the following criteria: worsening of oxygenation, increase in purulent tracheobronchial secretions, presence of fever (≥38.5°C) or hypothermia (≤36°C). Only microbiologically confirmed HAP was included: confirmation consisted of the isolation of a respiratory pathogen with at least 1+ semiquantitative growth of a good quality respiratory sample (defined as <3 squamous epithelial cells per low-power field) obtained within one calendar day prior or after clinical diagnosis of HAP. In our hospital, microbiological analysis of respiratory samples routinely consists of semiquantitative culture of endotracheal aspirate (ETA) in the ventilated patient or sputum in the non-intubated patient. For logistic reasons, bronchoalveolar lavage (BAL) is not systematically performed, similarly to current practice in the majority of European ICUs.[105] We

previously found that BAL and ETA had good qualitative and quantitative concordance in a cohort of patients with suspected ventilator-associated pneumonia (VAP). Positive and negative predictive values of a semiquantitative growth score of 1+ of a pathogen in ETA to identify the same pathogen in a quantity of at least 10^4 colony-forming units (CFU)/ml in BAL were 81% and 87%, respectively.[106] HAP was defined to be ventilator-associated if at the time of diagnosis, patients were under mechanical ventilation for 48 h or longer, or had been extubated for less than 48 h after mechanical ventilation for at least 2 days.

Development of the algorithms

The collected data were divided into a derivation and a validation cohort. The first 100 HAP episodes (1 July 2009 to 31 October 2010) made up the derivation cohort for the development of the local ecology based algorithm (LEBA) and the surveillance culture based algorithm (SCBA), both aiming to achieve a minimum of 85% appropriate coverage rate. For LEBA (Figure 11), we started from the clinical framework of the revised American Thoracic Society-Infectious Diseases Society of America (ATS-IDSA) guidelines and our previously recorded antimicrobial resistance patterns.[80] Clinical risk factors for MDR pathogens were defined as prior antimicrobial therapy during the current hospitalization, a hospital stay of 5 days or more, and previous hospitalization for 2 days or more in the preceding 6 months. SCBA (Figure 12) combined the same clinical risk factors for MDR with microbiological information from systematically collected SC. The SC consisted of oral, nasal and rectal swabs and urinary cultures upon admission, followed by thrice-weekly urinary and once-weekly oral, nasal and rectal samples in all patients, as well as thrice-weekly sputum in the non-intubated patient or ETA in the ventilated patient. In the case of positive respiratory SC (oral swabs or respiratory samples) 2 to 5 days before diagnosis of HAP, the antibiotic with the narrowest spectrum possible covering this (these) pathogen(s) was proposed (see also Table 8). In the absence of these, an alternative algorithm was proposed guided by clinical risk factors as in LEBA, but with upgrading to include all pathogens isolated from other SC collected within the last 6 months (respiratory SC more than 5 days before HAP and non-respiratory SC) (see also Figure 12). Both algorithms were retrospectively reviewed and compared with the actually prescribed antimicrobial therapy in the validation cohort.

Figure 11: Local ecology based algorithm

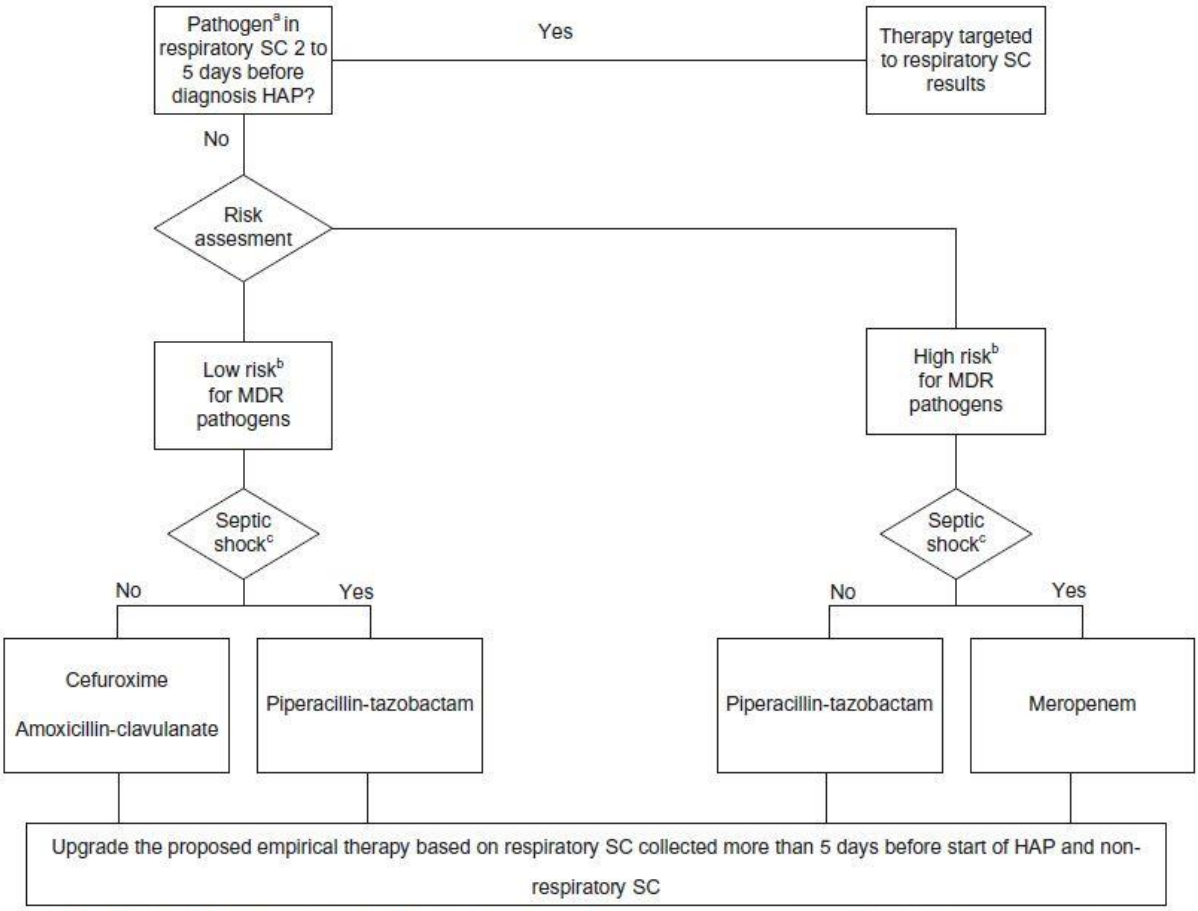


[a] Clinical risk assessment for multidrug-resistant pathogens: high risk if one of the following characteristics is present: prior antimicrobial therapy during the current hospitalization; current hospitalization ≥ 5 days; hospitalization for ≥2 days in the preceding 6 months.

[b] Septic shock was defined as systolic arterial blood pressure <90 mmHg or mean arterial blood pressure <65 mmHg despite adequate fluid resuscitation.

MDR, multidrug-resistant.

Figure 12: Surveillance culture based algorithm



[a] Respiratory pathogen defined as: *Acinetobacter spp.*, Enterobacteriaceae, *Haemophilus spp.*, *Pseudomonas spp.*, *Staphylococcus aureus*, *Stenotrophomonas spp.*, Streptococci.

[b] Clinical risk assessment for multidrug-resistant pathogens: high risk if one of the following characteristics is present: prior antimicrobial therapy during the current hospitalization; current hospitalization ≥5 days; hospitalization for ≥2 days in the preceding 6 months.

[c] Septic shock was defined as systolic arterial blood pressure <90 mmHg or mean arterial blood pressure <65 mmHg despite adequate fluid resuscitation.

SC, surveillance cultures; HAP, hospital-acquired pneumonia; MDR, multidrug-resistant.

Appropriateness and spectrum of antimicrobial therapy

We compared rates of appropriateness and spectrum between LEBA, SCBA and actually prescribed antimicrobial therapy by the treating physician. Therapy was considered appropriate when all pathogens involved in the HAP episode were covered by the antibiotic, or by at least one component of the antibiotic combination. To quantify the antimicrobial spectrum, we constructed a scale ranging from 1 - the most narrow-spectrum of empirical therapy, lacking anti-pseudomonal activity - to 5 - a combination therapy of two or more antibiotic agents (Table 8). We ranked fluoroquinolones higher than broad spectrum anti-pseudomonal beta-lactam antibiotics other than carbapemens, based upon the knowledge that exposure to fluoroquinolones is particularly associated with rapid emergence of MDR pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA),[140] and with *Clostridium difficile*-associated diarrhea,[141] and by our aim to preserve the use of fluoroquinolones for directed therapy of *Stenotrophomonas* spp. and *Pseudomonas aeruginosa*. In case of appropriate therapy, the antimicrobial spectrum was expressed as x steps in excess to the most narrow-spectrum therapy possible covering all causative pathogens isolated in the HAP episodes.

Table 8: Scale quantifying the spectrum of the antibiotic treatment

Step 1	• Non-antipseudomonal penicillins (amoxicillin-clavulanate) • Second generation or third generation non-antipseudomonal cephalosporins (cefuroxime, ceftriaxone) • Trimethoprim/sulfamethoxazole
Step 2	• Anti-pseudomonal penicillins (piperacillin-tazobactam) • Third generation anti-pseudomonal cephalosporins (ceftazidime)
Step 3	• Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)
Step 4	• Anti-pseudomonal carbapenems (meropenem)
Step 5	• Combination therapy of two or more antibiotic agents

Statistics

Continuous variables are described as mean (±standard deviation) or median (interquartile range) for normal or non-normal distribution, respectively. To compare paired proportions the McNemar test for related samples was used. Differences in medians were checked using the Wilcoxon signed-rank test. All statistical analyses were performed with SPSS® software (SPSS, version 21, Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

4.C.4 Results

All data reported apply to the validation cohort of 113 episodes of HAP, including 52 (46%) episodes of VAP, registered between 1 November 2010 and 31 October 2012 in 104 patients. There was need for subsequent mechanical ventilation in 39/61 (64%) of the non-VAP patients. The median age of the patients was 64 years (54 to 74), and 74% were male. In 99 (87.6%) of the HAP episodes, clinical risk factors for MDR pathogens were present: prior antibiotics in 81%, current hospitalization for 5 days or more or hospitalization in the previous 6 months in 82%. Septic shock was present in 23% of the HAP episodes. The length of ICU stay following diagnosis of HAP was 10 days (6 to 22) when appropriate antibiotics were administered, 7 days (2 to 16) if the prescribed antibiotics were inappropriate ($P = 0.10$). The overall ICU mortality was 30.1% and did not differ between patients with or without appropriate antimicrobial therapy (28.4% versus 38.9%, $P = 0.375$).

A total of 140 pathogens were isolated, 84% of which were Gram-negative bacteria (Table 9). HAP was mono-microbial in 89 (79%) and poly-microbial in 24 (21%) episodes.

Table 9: Pathogens (n=140) associated with HAP

Pathogen	n (%)
Gram-positive bacteria	
Staphylococcus aureus	14 (10%)
MRSA	7
Streptococcus pneumoniae	5 (3.6%)
Other streptococci	1 (0.7%)
Gram-negative bacteria	
Enterobacteriaceae	**70 (50%)**
Escherichia coli	31 (22.1%)
Enterobacter sp.	13 (9.3%)
Klebsiella sp.	12 (8.6%)
Serratia sp.	6 (4.3%)
Morganella morganii	4 (2.9%)
Citrobacter sp.	2 (1.4%)
Hafnia alvei	1 (0.7%)
Proteus sp.	1 (0.7%)
ESBL- producing enterobacteriaceae	8
Non-fermenters	**35 (25%)**
Pseudomonas aeruginosa	27 (19.3%)
Ceftazidim resistance	7
Carbapenem resistance	9
Stenotrophomonas maltophilia	5 (3.6%)
*Acinetobacter baumannii**	3 (2.1%)
Other gram-negative bacteria	
Haemophilus influenzae	12 (8.6%)
Moraxella catarrhalis	3 (2.1%)
Total	140

HAP, hospital-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, Extended-spectrum beta-lactamase producing enterobacteriaceae

* All *Acinetobacter baumannii* isolates were third generation cephalosporin resistant and carbapenem sensitive

Appropriateness and spectrum of antimicrobial therapy

Appropriate antibiotic therapy was prescribed in 95 (84.1%) HAP episodes. Antimicrobial choices proposed by LEBA and SCBA were appropriate in 88.5% and 87.6%, respectively. Paired analysis showed no significant difference in adequacy for the different strategies (prescribed therapy versus LEBA: $P = 0.33$; prescribed therapy versus SCBA: $P = 0.5$; LEBA versus SCBA: $P = 0.99$). Pathogens associated with inadequate empirical therapy are detailed in Table 10.

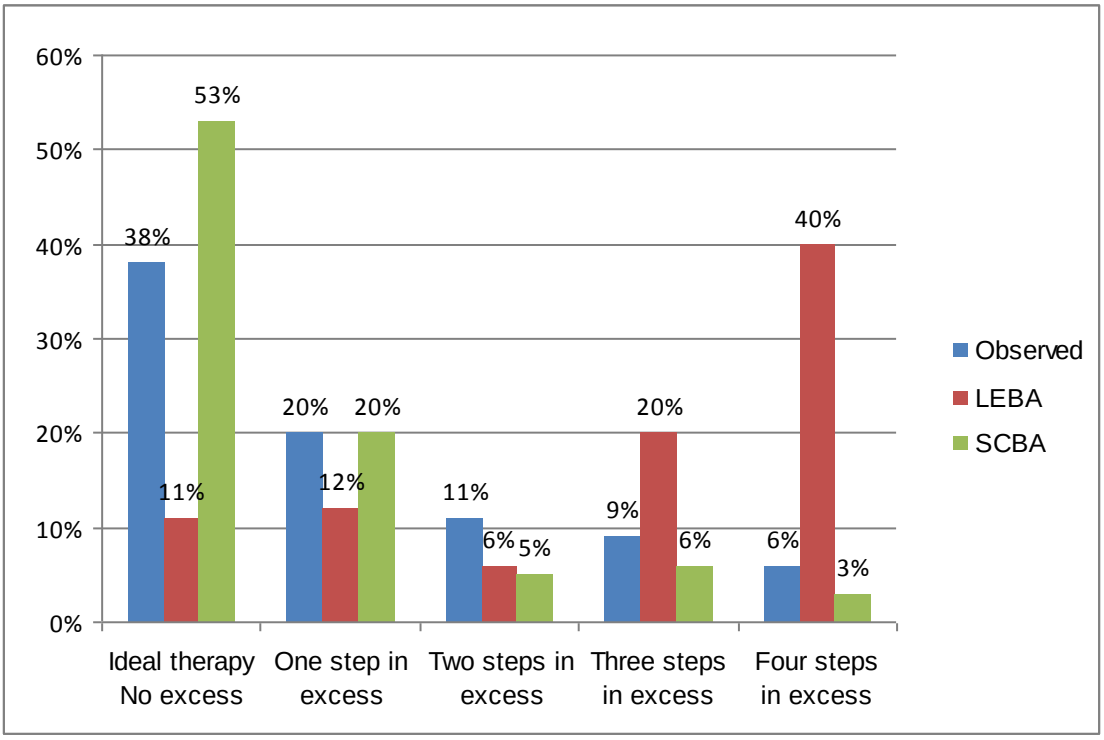
Table 10: Pathogens associated with inadequate empirical therapy

Pathogen	Prescribed therapy	LEBA	SCBA
Acinetobacter baumannii	3	-	1
Escherichia coli	4	-	2
Enterobacter sp.	2	-	-
Klebsiella sp.	-	-	1
MRSA	-	4	3
Pseudomonas aeruginosa	4	3	4
Serratia sp.	2	2	2
Stenotrophomonas maltophilia	3	5	2

MRSA, methicillin-resistant *Staphylococcus aureus*

In significantly more episodes, SCBA proposed antibiotics of a narrower spectrum as compared to both the prescribed therapy and the regimen suggested by LEBA ($P < 0.001$) (Figure 13). Significantly less combination therapy was proposed by SCBA (7.1%) in comparison with LEBA (81.4%) ($P < 0.001$). SCBA recommended carbapenems in significantly fewer episodes than LEBA (24 (21.2%) versus 92 (81.4%), respectively ($P < 0.001$)).

Figure 13: Evaluation of the spectrum of antimicrobial therapy



LEBA: Local ecology based algorithm; SCBA: surveillance culture based algorithm

LEBA: 3 (1.25-4) steps in excess; SCBA: 0 (0-1) steps in excess; Prescribed therapy: 1 (0-2) steps in excess

Surveillance culture based algorithm

Respiratory SC sampled 2 to 5 days before HAP onset were available in 63 episodes (55.8%) of HAP, of which 43 (68%) grew at least one pathogen. As such, SCBA suggested targeted antimicrobial therapy in 43/113 (38.1%) of HAP episodes: HAP for which targeted therapy was suggested was ventilator-associated in 72% (31/43), occurred more than 5 days after ICU admission in 77% (33/43) and was caused by the following pathogens (n = 53): *S. aureus* (6/53, 3 methicillin-susceptible *S. aureus* and 3 MRSA), *S. pneumoniae* (1/53), *Enterobacteriaceae* (29/53), *P. aeruginosa* (10/53), other Gram-negative bacteria (7/53). Recent respiratory SC accurately predicted all causative pathogens in 81.4% (35/43) of HAP; SCBA-targeted antimicrobial therapy would appropriately cover all causative pathogens (including those not predicted by SC) in 93% (40/43) of cases.

In the case of negative or absent respiratory SC 2 to 5 days before start of HAP (n = 70, 61.9%), SCBA took into account both respiratory SC more than 5 days prior to infection and non-respiratory SC. In 28/70 (40%) of these HAP episodes positive SC were available, leading to upgrading of the proposed empirical therapy in 13/70 HAP (19%) and a switch from

inappropriate to appropriate antibiotic proposals in 10 episodes. By not upgrading our therapy in these cases our rate of appropriate antibiotic therapy would have dropped from 87.6% to 78.8%.

4.C.5 Discussion

Both guidance by SC as well as the use of ICU-specific empirical schemes that incorporate local microbiology data have been shown to increase appropriate empirical prescription and reduce the use of broad-spectrum antimicrobials as compared to general guidelines.[80, 84, 136, 137, 142, 143] Our study is the first to demonstrate the benefit of SC in surplus to tailoring guidelines to local susceptibility data. We found that incorporating results of SC (SCBA) in a clinical algorithm (LEBA) to help the choice of an empirical antibiotic regimen in suspected HAP would allow reduction in the use of broad-spectrum antimicrobials for equal rates of appropriate coverage. In particular, a 60% decrease in the empirical use of carbapenems would be attained, which is an important achievement in terms of antibiotic stewardship. Similarly, as compared to actually prescribed antibiotics, which were at the discretion of the attending physician with access to SC results but without guidance by a treatment algorithm, stricter adherence to SCBA would lead to further constraint of empirical use of broad-spectrum drugs. We measured the expenditure of antibiotics in terms of extension of spectrum by ranking antimicrobial classes along a scale of increasingly broad antimicrobial coverage. While this scale artificially translates a complex phenomenon into a simplified score, it allows some quantification of ecological selection pressure between different antibiotic schemes.

Two observations underlie the construction of SCBA. First, previously we found high negative predictive values of negative SC for the presence of MDR pathogens in HAP,[87] allowing a narrower-spectrum antibiotic even in patients with clinical risk factors for MDR. Second, we followed the paradigm that ICU-acquired pneumonia is often preceded by colonization of the upper and lower airways by the same pathogen, going through a possible intermediate stage of ventilator-associated tracheobronchitis.[144] Following Bayes' theorem, the positive and negative predictive values of SC were then applied to the ATS-IDSA guideline-based clinical risk categories for MDR HAP. Although there are no reports suggesting resistant micro-organisms cause more septic shock, we opted for broader therapy in these cases to minimize the risk of harm caused by inappropriate therapy.

In hospital-acquired infection, narrowing the spectrum of antibiotic therapy is usually done as de-escalation following an initially broad-spectrum therapy aimed at maximal chance for appropriate coverage. However, limiting antimicrobial therapy upfront may offer several

advantages. First, aminoglycosides and glycopeptides, which carry an important toxicity profile,[145, 146] were abandoned in the SCBA if there were no SC results supporting their need. A study in patients with pneumonia found increased mortality in patients who were treated with strict adherence to the ATS-IDSA guideline, including the recommendations for combination therapy, as compared to patients in whom treatment deviated from the recommendations.[147] The authors proposed the toxic effects of combination antimicrobial therapy as a potential explanation. Second, although prolonged exposure to antibiotic therapy has been clearly associated with the emergence of resistance,[148] there is no proof that a short course is ecologically harmless and devoid of selection pressure. Finally, there exists a gap between the concept of de-escalation and what is achieved in practice. In several observational studies, the authors found rates of de-escalation to be fairly low,[149-151] with lack of an identifiable microbial agent as the main barrier. SCBA partially circumvents this, as in case of negative diagnostic cultures and SC, a narrower spectrum empirical therapy, is recommended as compared to LEBA.

Restricting the number of empirical combination therapies will reduce direct antibiotic costs. On the other hand one fulltime-equivalent microbiology laboratory technician is assigned to process SC of all patients admitted to our 36-bed ICU and the cost for the laboratory material is estimated at 33 euro per week. However, not all of this cost is exclusively for surveillance purposes, as few additional respiratory cultures for diagnostic purposes are required under this SC regime. Additionally, it can be argued that SC are a cornerstone in infection control in settings where MDR pathogens are endemic and that their guidance of antibiotic therapy is only an added benefit.[152, 153]

A number of limitations have to be addressed. First, our study is evidently monocentric and our SCBA is site-specific. However, the concept of SCBA may be more universally applicable, as the predictive values of SC as reported in several recent studies are fairly consistent, provided that SC are regularly and at least twice weekly sampled.[84] Our SCBA could serve as a template, which has to be translated into antibiotic recommendations depending on local ecology and carefully assessed before implementation. Second, resistance rates are moderate in our setting and the added value of SC in combination with guidelines tailored to local susceptibility data has to be re-evaluated in settings with higher resistance rates. As targeted antimicrobial therapy was proposed by SCBA in more than one third of HAP episodes, we suspect that implementing this algorithm would also lead to reduction in empirical broad-spectrum combination antibiotic therapy in these high-resistance environments. Third, it would be safe to regularly test the algorithms in order to match potentially changing ecology. Fourth, this analysis was performed retrospectively, subsequently the algorithms and adherence by the treating physicians to the algorithms have not been evaluated in practice. As such, the performance of the algorithms may

in reality be different from what is anticipated. Finally, our study design does not allow us to conclude whether an empirical strategy with de-escalation, as compared to a strategy that is more targeted to colonizing pathogens translates into a different patient outcome or microbiological selection pressure.

Conclusion

As compared to an algorithm based upon clinical risk factors for MDR and adapted to local susceptibility results, an algorithm with additional guidance from SC could achieve comparably high rates of appropriate coverage with the use of fewer broad-spectrum antibiotics. Antibiotic therapy specifically targeted to respiratory pathogens identified in recent SC would be possible in 38% of HAP episodes. SC guided algorithms may constitute a component of antibiotic stewardship programs. Additional studies should be performed in ICU settings with higher levels of antibiotic resistance.

Key messages

- Addition of surveillance culture results in empirical antibiotic treatment algorithms for hospital-acquired pneumonia could restrict the use of broad-spectrum antimicrobial drugs.
- Targeting empirical treatment to recent respiratory surveillance cultures could be achieved in more than one third of hospital-acquired pneumonia.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LDB conceived, designed and coordinated the study, performed data acquisition and analyses and drafted the manuscript, LS performed data acquisition and analyses and critically revised the manuscript for important intellectual content, BG contributed to data acquisition and analyses and critically revised the manuscript for important intellectual content, JB contributed to data acquisition and analyses and critically revised the manuscript for important intellectual content, GC contributed to data acquisition and analyses and critically revised the manuscript for important intellectual content, JDW contributed to data acquisition and analyses and

critically revised the manuscript for important intellectual content, DB contributed to data acquisition and analyses and critically revised the manuscript for important intellectual content, JD contributed to data acquisition and analyses and critically revised the manuscript for important intellectual content, PD conceived, designed and coordinated the study, performed data acquisition and analyses and drafted the manuscript.

All authors read and approved the final manuscript. All authors agree to be fully accountable for the content of this work.

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D. IMPACT OF DE-ESCALATION OF BETA-LACTAM ANTIBIOTICS ON THE EMERGENCE OF ANTIBIOTIC RESISTANCE IN ICU PATIENTS: A RETROSPECTIVE OBSERVATIONAL STUDY

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4.D.1 Abstract

Purpose:

Antibiotic de-escalation is promoted to limit prolonged exposure to broad-spectrum antibiotics, but proof that it prevents the emergence of resistance is lacking. We evaluated determinants of antibiotic de-escalation in an attempt to assess whether the latter is associated with a lower emergence of antimicrobial resistance.

Methods:

Antibiotic treatments, starting with empirical beta-lactam prescriptions, were prospectively documented during 2013 and 2014 in a tertiary intensive care unit (ICU) and categorized as continuation, de-escalation or escalation of the empirical antimicrobial treatment. Determinants of the de-escalation or escalation treatments were identified by multivariate logistic regression; the continuation category was used as the reference group. Using systematically collected diagnostic and surveillance cultures, we estimated the cumulative incidence of antimicrobial resistance following de-escalation or continuation of therapy, with adjustment for ICU discharge and death as competing risks.

Results:

Of 478 anti-pseudomonal antibiotic prescriptions, 42 (9 %) were classified as escalation of the antimicrobial treatment and 121 (25 %) were classified as de-escalation, mainly through replacement of the originally prescribed antibiotics with those having a narrower spectrum. In multivariate analysis, de-escalation was associated with the identification of etiologic pathogens ($p < 0.001$). The duration of the antibiotic course in the ICU in de-escalated versus continued prescriptions was 8 (range 6–10) versus 5 (range 4–7) days, respectively ($p < 0.001$). Mortality did not differ between patients in the de-escalation and continuation categories. The cumulative incidence estimates of the emergence of resistance to the initial beta-lactam antibiotic on day 14 were 30.6 and 23.5 % for de-escalation and continuation, respectively ($p = 0.22$). For the selection of multidrug-resistant pathogens, these values were 23.5 (de- escalation) and 18.6 % (continuation) respectively ($p = 0.35$).

Conclusion:

The emergence of antibiotic-resistant bacteria after exposure to anti-pseudomonal beta-lactam antibiotics was not lower following de-escalation.

Keywords:

Beta-lactam antibiotics, Antibiotic stewardship, Multidrug-resistance, De-escalation, Information technology system

4.D.2 Introduction

Selection of the appropriate antimicrobial therapy for critically ill patients is challenging in the context of the increasing prevalence of antimicrobial resistance. International and local guidelines advocate the use of broad-spectrum antibiotics in severe healthcare-associated infections for maximal empirical coverage, coupled with antibiotic de-escalation to reduce overall exposure to broad-spectrum antibiotics and its detrimental ecological effects.[90, 91] De-escalation may be achieved through replacing broad-spectrum antibiotics by narrow-spectrum drugs, through stopping components of an antibiotic combination, or by early withdrawal of antibiotics in the absence of infection.[90, 92, 93, 96, 154-156] The widely promoted strategy of de-escalation is backed up by only a few studies which used heterogeneous definitions of de-escalation and provided equivocal results.[93, 96] The survival benefit related to de-escalation which was reported in some observational trials [157-159] could not be confirmed in other studies [160, 161], nor in a recent multicenter randomized trial,[95] although none showed increased mortality associated with de-escalation. Furthermore, there is a lack of microbiological data in support of the presumption that de-escalation limits the emergence of multidrug-resistant (MDR) pathogens.[93]

In the observational study reported here, we describe treatment changes (de-escalation and escalation) following empirical beta-lactam antibiotic prescription in intensive care unit (ICU) patients and identify determinants of the different treatment patterns. We subsequently relate these patterns to patient outcome, focusing on the effect of de-escalation of anti-pseudomonal beta-lactam antibiotics on the emergence of antibiotic resistance.

4.D.3 Materials and methods

The study was conducted at the 14-bed medical ICU and the 22-bed surgical ICU (SICU) of Ghent University Hospital (1056 beds). From 1 January 2013 to 31 December 2014, we prospectively registered all infections requiring antibiotics with the aid of the software application COSARA (Computer-based Surveillance and Alerting of infections, Antimicrobial Resistance and Antibiotic consumption in the ICU), developed in collaboration with the Department of Information Technology of Ghent University.[102, 124] COSARA facilitates the build-up of an

extensive data warehouse by allowing linkage between automatically collected clinical and biochemical variables, antimicrobial prescription data, microbiology results and clinical diagnoses of infection. During the study period, no strict empirical antibiotic protocol was used, and all empirical choices and subsequent changes were at the liberty of the senior ICU-physician, working together in close collaboration with microbiologists and conferring three times weekly. As described previously,[162] empirical antibiotic choices are essentially guided by systematically collected surveillance cultures (SC). Piperacillin–tazobactam, ceftazidime, and meropenem were administered as a continuous infusion, and non-antipseudomonal beta-lactam antibiotics and non-beta-lactam antibiotics were administered intermittently. Standard dosing regimens are provided in Electronic Supplemental Material (ESM) Table 1.

From the COSARA data warehouse, we retrospectively analyzed all beta-lactam antibiotic courses of at least a 48 h duration that were prescribed as first-line treatment of an infection. Only episodes in the ICU of at least a 96 h duration were included as antibiotic changes were unlikely to occur in shorter episodes. Antibiotic changes were classified as de-escalation or escalation depending on whether the changes represented a move up or down, respectively, a predefined ranking system of agents according to increasing order of Gram-negative antimicrobial activity (ESM Table 1). Roughly outlined, this ranking system was: step 1: "beta-lactam antibiotics without anti-pseudomonal activity or fluoroquinolones advocated as empirical treatment for severe community-acquired infection"; step 2: "non-carbapenem beta-lactam antibiotics with anti-pseudomonal activity or fluoroquinolones targeted at *Pseudomonas*"; step 3: "carbapenems"; step 4: "carbapenems in combination with a second antibiotic with Gram-negative coverage". We did not evaluate changes in Gram-positive coverage (such as adding or withholding glycopeptides or linezolid). The ranking system was modified according to the focus of infection and the consequent need for anaerobic coverage (for example, as required in complicated intra-abdominal infections). Levofloxacin was classified as a step 1 antibiotic despite the anti-pseudomonal activity as it is a recommended treatment choice for severe community-acquired infections in national guidelines.[163]

Electronic Supplementary Material - Table 1a: Ranking of agents by increasing order of Gram-negative antimicrobial activity: no need for anaerobic coverage; e.g. respiratory, urinary, catheter infection (standard dosing)

Step 1	• Non-antipseudomonal penicillins ▪ ampicillin (1g q4h) ▪ amoxicillin-clavulanate (1g q6h) ▪ temocillin (2g q8h) • Second generation or third generation non-antipseudomonal cephalosporins o cefuroxime (1.5g q8h) o ceftriaxone (1g q12h or 2g q12h in case of meningitis) o cefotaxime (2g q8h) • Fluoroquinolones o levofloxacin (500mg q12h) o moxifloxacin (500mg q24h) • Trimethoprim/sulfamethoxazole (160mg/800mg q12h)
Step 2	• Anti-pseudomonal penicillins: piperacillin-tazobactam (16g over 24h) • Third generation anti-pseudomonal cephalosporins: ceftazidime (6g over 24h) • Fluoroquinolones: ciprofloxacin (400mg q8h)
Step 3	• Anti-pseudomonal carbapenems: meropenem (3g over 24h)
Step 4	• Anti-pseudomonal carbapenems (meropenem) + other antibiotic with Gram-negative coverage

Electronic Supplementary Material - Table 1b: Ranking of agents by increasing order of Gram-negative antimicrobial activity: need for anaerobic coverage; e.g. complicated abdominal infection (standard dosing)

Step 1	• Non-antipseudomonal penicillins: amoxicillin-clavulanate • Fluoroquinolones o levofloxacin + metronidazole (500mg q8h) o moxifloxacin • Tigecycline (50mg q12h)
Step 2	• Anti-pseudomonal penicillins: piperacillin-tazobactam • Third generation anti-pseudomonal cephalosporins: ceftazidime + metronidazole • Fluoroquinolones: ciprofloxacin + metronidazole
Step 3	• Anti-pseudomonal carbapenems: meropenem
Step 4	• Anti-pseudomonal carbapenems (meropenem) + other antibiotic with Gram-negative coverage

We registered patient demographics, co-morbidities, focus and severity of the infection, and daily sequential organ failure assessment (SOFA) scores. Microbiology results from 10 days prior to ICU admission until 10 days following ICU discharge were taken into consideration, comprising SC and additional cultures upon clinical suspicion of infection. SC consisted of oral, nasal, and rectal swabs upon admission, followed by once-weekly nasal samples and twice-weekly oral and rectal samples in all patients, as well as twice weekly sputum in the non-intubated patient or endotracheal aspirate in the ventilated patient. Cultured pathogens were classified as etiologic if these were considered to represent the causal pathogen of the infection and as colonizing in other cases. In case of microbiologically documented infection, antibiotic treatment was considered to be appropriate if all etiologic pathogens were covered.

For the outcome analysis, patients were included once, and the first beta-lactam prescription was considered. The following outcome parameters were recorded: ICU mortality, in-hospital mortality, subsequent infections requiring antibiotic therapy, and total antibiotic consumption in the ICU, defined as the total number of days that a patient received an antibiotic during his/her stay in the ICU. In case of combination therapy, the total antibiotic consumption equaled the sum of the number of days of the individual components of the treatment. Antibiotic-free days were noted in the subgroup of patients with a length of stay (LOS) in the ICU of at least 14 days. In addition, emergence of pathogens resistant to the initial beta-lactam antibiotic and emergence of MDR pathogens was registered. Pathogens isolated in any culture from day 2 following the start of the antibiotic treatment under study and not present before that time were defined as having emerged after treatment. The following pathogens were categorized as MDR: methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *enterococcus*, *Stenotrophomonas maltophilia*, *Achromobacter* spp., MDR *Enterobacteriaceae*, MDR *Pseudomonas aeruginosa*, and MDR *Acinetobacter* spp. modified from the publication of Magiorakos et al., in accordance with the MDR definition employed by the multicenter research project R-GNOSIS, work package 6 (ESM Table 2).[164, 165] In addition, we included *Enterobacteriaceae* resistant for both 3rd generation cephalosporins and piperacillin-tazobactam and *Clostridium difficile*.

Electronic Supplementary Material - Table 2:

Defining MDR *Enterobacteriaceae,* MDR *Pseudomonas aeruginosa* and MDR *Acinetobacter* spp.

MDR *Enterobacteriaceae*

• *Enterobacteriaceae* resistant against at least three antibacterial agents from the below listed groups:
  ○ Ciprofloxacin
  ○ Amikacin
  ○ Gentamycin
  ○ Piperacillin-tazobactam
  ○ Cefotaxime or ceftriaxone
  ○ Trimethoprim-sulfamethoxazole
• Meropenem or colistin resistant *Enterobacteriaceae*
• Extended-spectrum beta-lactamase producing *Enterobacteriaceae*
• Carbapenemase producing *Enterobacteriaceae*

MDR *Pseudomonas aeruginosa*

• *Pseudomonas aeruginosa* resistant against at least three antibacterial agents from the below listed groups or to meropenem and one other agent of the below listed groups:
  ○ Piperacillin-tazobactam
  ○ Ceftazidime
  ○ Gentamycin
  ○ Amikacin
  ○ Ciprofloxacin
• Colistin resistant *Pseudomonas aeruginosa*

MDR *Acinetobacter* spp.

• *Acinetobacter* spp. resistant against at least three antibacterial agents from the below listed groups:
  ○ Piperacillin-tazobactam
  ○ Ceftazidime
  ○ Gentamycin
  ○ Amikacin
  ○ Ciprofloxacin
• Meropenem or colistin resistant *Acinetobacter* spp.

Used by permission of Prof. Marc Bonten, coordinator of the multicenter research project R-GNOSIS, work package 6; MDR, multidrug-resistant.

The Ghent University Hospital Ethics Committee approved the study (registration number B670201524161) and waived informed consent. Only patients aged 16 years or older were included.

Statistics

Categorical variables were expressed as frequencies (percentages), continuous variables were described as median values with the interquartile range (IQR; 25–75th percentile). Continuation of the antibiotic treatment was defined as the standard to which de-escalation and escalation were compared. Differences in categorical variables were calculated using Pearson Chi-square test or Fisher's exact test as appropriate. The Mann–Whitney *U* test was used to compare continuous variables. A multivariate logistic regression model was used to identify factors associated with de-escalation and escalation. All variables with a *p* value of 0.15 or lower and considered to be clinically important were entered into the model. The Hosmer–Lemeshow test was used to evaluate goodness-of-fit. Statistical significance was defined as $p < 0.05$. As systematic SC are no longer performed in patients discharged from ICU or in patients who die during their stay in the ICU, and hence the non-informative censoring assumption is likely to be violated, a competing risk analysis was performed when estimating the cumulative incidence of the emergence of antibiotic resistance.[166-168] Cumulative incidence functions (CIFs) of de-escalation and continuation were compared using a modified Chi-square test, with statistical significance defined as $p < 0.05$.[169] All statistical analyses were performed with SPSS® software (SPSS, version 23; IBM Corp., Armonk, NY), and the R 3.2.2 software package.[170] The competing risk analysis was performed using the "cuminc" routine available in the "cmprsk" package developed by Gray.[171]

4.D.4 Results

In total, we included 782 prescriptions of beta-lactam antibiotics for 615 patients in our analysis. Changes that could not be categorized as de-escalation or escalation [n = 50 (6.4%)] were omitted from the analysis. Of the remaining prescriptions (n = 732), 254 (35 %) had no anti-pseudomonal activity [amoxicillin–clavulanate, n = 178 (24 %); cefuroxime, n = 53 (7 %), ceftriaxone n = 23 (3 %)]. Piperacillin–tazobactam was the most frequently used anti-pseudomonal antibiotic [n = 343 (47 %)], followed by meropenem [n = 111 (15 %)] and ceftazidime [n = 24 (3 %)]. Treatment changes are detailed in Fig. 14a, b. Anti-pseudomonal beta-lactam antibiotics were de-escalated in 25 % of the treatments and escalated in 9 %; subsequent changes occurred in 26 % of treatments; de-escalation was maintained in 81 % of the treatment courses. Initial beta-lactam therapy was continued during the entire treatment course in 66 % of treatments; 67 % of continued treatments for microbiologically documented infections could have been de-escalated based on susceptibility data of the etiologic pathogen.

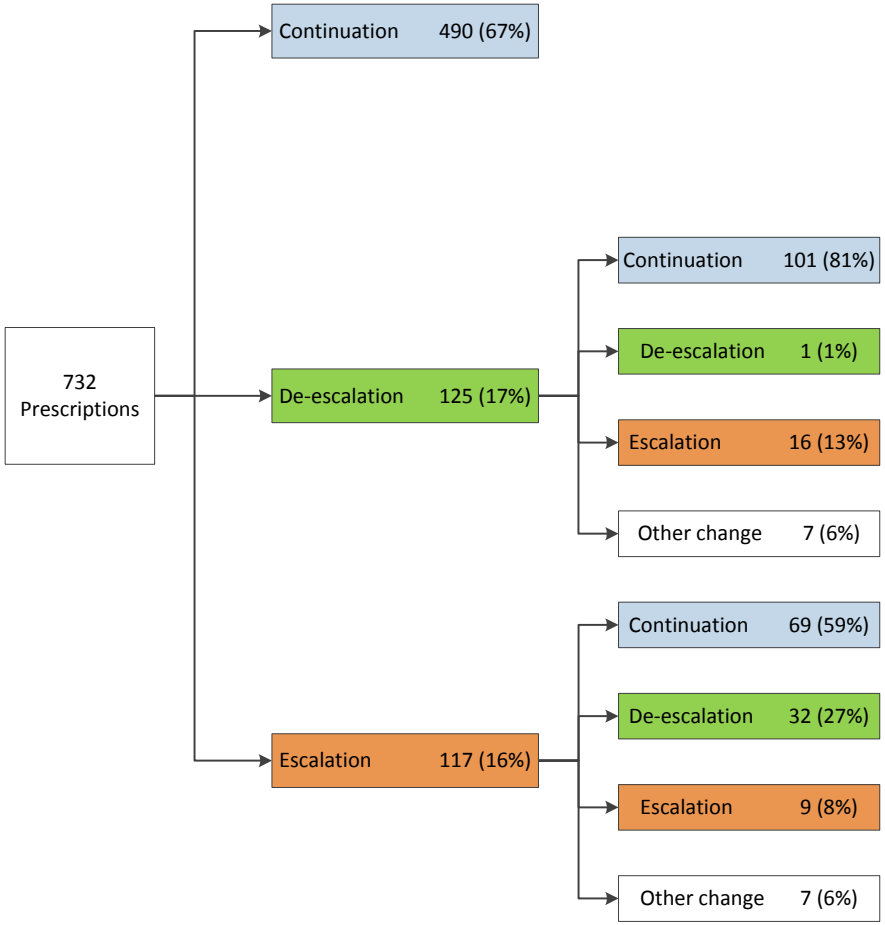


Figure 14a: Treatment changes subsequent to the initial beta-lactam antibiotic prescription (all beta-lactam prescriptions included)

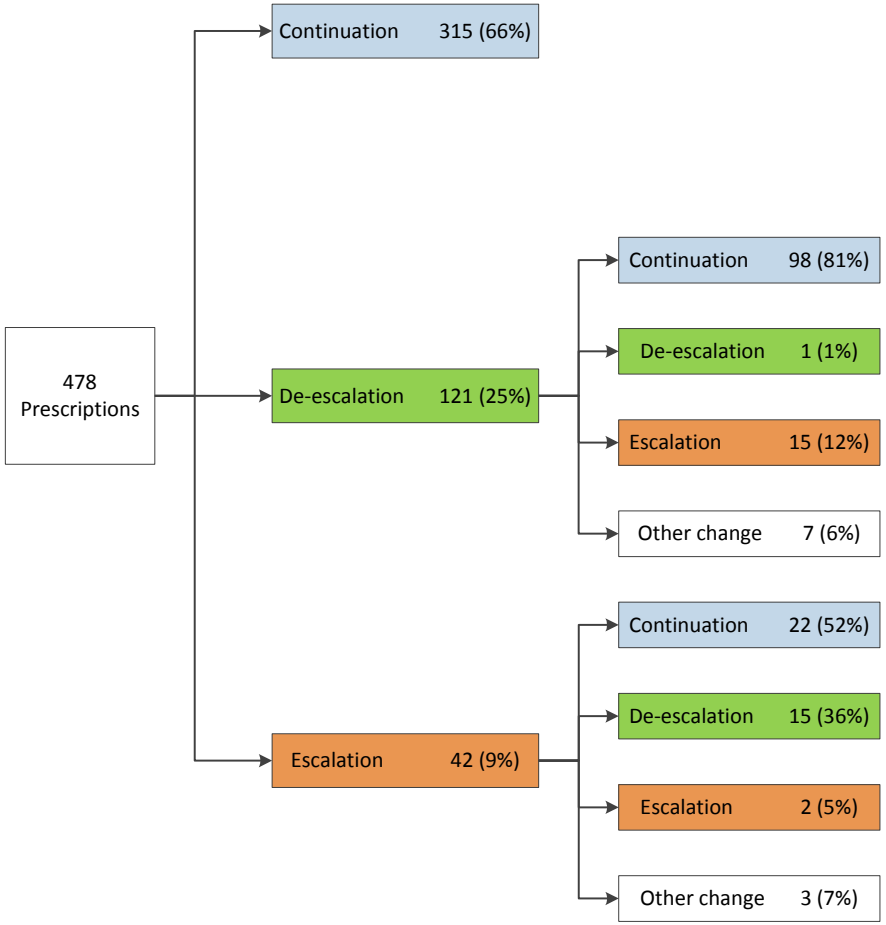


Figure 14b: Treatment changes subsequent to the initial beta-lactam antibiotic prescription (only beta-lactam prescriptions with activity against *Pseudomonas* included)

Determinants of de‑escalation and escalation

To identify the determinants of de-escalation and escalation we included prescriptions with anti-pseudomonal activity only (n = 478). The median time interval to antibiotic change was 3 days (IQR for de-escalation and escalation was 3–5 and 2–7 days, respectively). De-escalation was achieved by narrowing the Gram-negative spectrum in 111 treatments, by reducing the number of antimicrobials in three treatments, and by a combination of both in seven treatments. In 63 % of de-escalations the empirical beta-lactam antibiotic was changed to another beta-lactam antibiotic. Levofloxacin was the most frequently prescribed non-beta-lactam antibiotic in the case of de-escalation (21 %) (Tables 11, 12)

Factors associated with de-escalation or escalation are detailed in Table 12. In the multivariate analysis, de- escalation was significantly associated with the identification of etiologic pathogens ($p < 0.001$), and escalation of therapy was significantly associated with severe sepsis or septic shock at presentation ($p = 0.03$), worsening SOFA score ($p = 0.008$), the presence of additional (non-etiologic) isolates resistant to the initial antibiotic ($p = 0.01$), admission to the SICU ($p = 0.003$) and hospitalization duration prior to start of the infection ($p = 0.04$).

Table 11: Baseline characteristics and univariate analysis on determinants of de-escalation and escalation of anti-pseudomonal beta-lactam therapy*

	Treatment				*P* value	
	Total n=453	Con-tinuation n=307; 68%	De-escalation n=111; 25%	Escalation n=35; 8%	De-escalation vs. Cont.	Escalation vs. Cont.
Baseline characteristics						
Age (years)	63 [49-72]	63 [50-72]	61 [45-72]	65 [53-72]	0.47	0.76
Male sex	319 (70.4%)	211 (68.7%)	80 (72.1%)	28 (80%)	0.51	0.17
Apache II score[a]	23 [18-29]	22 [17-28]	23 [18-30]	23 [20-31]	0.31	0.34
SAPS II score[b]	56 [42-71]	56 [42-70]	59 [45-73]	56 [41-74]	0.14	0.66
Hospitalisation duration prior to initiation of BL therapy (days)	7 [3-19]	9 [4-23]	6 [2-15]	3 [1-9]	0.008	<0.001
Antibiotic exposure during ICU stay prior to initiation of BL therapy	197 (43.5%)	150 (48.9%)	39 (35.1%)	8 (22.9%)	0.01	0.003
ICU department					0.05	0.001
• Medical ICU	198 (43.7%)	149 (48.5%)	42 (37.8%)	7 (20%)		
• Surgical ICU	255 (56.3%)	158 (51.5%)	69 (62.2%)	28 (80%)		
Co-morbidities						
• Diabetes	76 (17.8%)	47 (16.2%)	19 (18.3%)	10 (30.3%)	0.62	0.04
• Hypertension/ peripheral vascular disease	188 (44.2%)	123 (42.6%)	50 (48.5%)	15 (45.5%)	0.29	0.75
• Coronary disease	82 (19.4%)	52 (18.1%)	23 (22.5%)	7 (21.2%)	0.33	0.66
• Chronic kidney disease	86 (20.3%)	62 (21.5%)	22 (21.4%)	2 (6.3%)	0.98	0.04
• Malignancy	97 (22.7%)	68 (23.4%)	22 (21%)	7 (21.2%)	0.6	0.77
• Chronic respiratory disease	84 (20%)	59 (20.8%)	18 (17.5%)	7 (21.9%)	0.47	0.89
Infection characteristics						
Initial BL therapy					0.02	0.4
• Ceftazidime	24 (5.3%)	20 (6.5%)	3 (2.7%)	1 (2.9%)		
• Piperacillin-tazobactam	327 (72.2%)	225 (73.3%)	72 (64.9%)	30 (85.7%)		
• Meropenem	102 (22.5%)	62 (20.2%)	36 (32.4%)	4 (11.4%)		
Focus of infection					0.2	0.03
• Abdominal	91 (20.1%)	51 (16.6%)	25 (22.5%)	15 (42.9%)		
• Catheter related	6 (1.3%)	2 (0.7%)	4 (3.6%)	0		
• Respiratory	247 (54.5%)	174 (56.7%)	59 (53.2%)	14 (40%)		
• Skin and soft tissue	16 (3.5%)	12 (3.9%)	4 (3.6%)	0		
• Urinary	19 (4.2%)	14 (4.6%)	4 (3.6%)	1 (2.9%)		
• Other	74 (16.3%)	54 (17.6%)	15 (13.5%)	5 (14.3%)		
Severe sepsis/septic shock	178 (39.4%)	115 (37.5%)	42 (38.2%)	21 (60%)	0.89	0.01
ΔSOFA[c]	0 [-1,2]	0 [-1, 2]	1 [-1,2]	-1 [-4,1]	0.35	0.001
Bacteremia	36 (8.4%)	19 (6.6%)	13 (12.1%)	4 (11.4%)	0.07	0.29
Microbiologically documented infection	215 (47.5%)	116 (37.8%)	80 (72.1%)	19 (54.3%)	<0.001	0.06
Presence of (non-etiologic) isolates resistant to the initial BL therapy	124 (27.4%)	71 (23.1%)	39 (35.1%)	14 (40%)	0.01	0.03
• in microbiologically documented infection (n=215)	77/215 (35.8%)	39/116 (33.6%)	31/80 (38.8%)	7/19 (36.8%)	0.46	0.78
• in non-microbiologically documented infection (n=238)	47/238 (19.7%)	32/191 (16.8%)	8/31 (25.8%)	7/16 (43.8%)	0.22	0.008

*patients with inadequate empirical therapy in microbiologically documented infections were excluded for analysis; [a] Apache II score, Acute Physiology and Chronic Health Evaluation score; [b] SAPS II score, Simplified Acute Physiology Score; BL therapy, beta-lactam therapy; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score. [c] ΔSOFA is SOFA score on day 0 minus SOFA score on day 2 of infection.

Table 12: Multivariate analysis on determinants of de-escalation and escalation of anti-pseudomonal beta-lactam therapy

	De-escalation versus continuation		Escalation versus continuation	
	Adjusted OR (95% CI)*	*P* value	Adjusted OR (95% CI)**	*P* value
ICU department (medical/surgical ICU)	0.81 (0.5-1.3)	0.39	0.24 (0.1-0.61)	0.003
Hospitalisation duration prior to initiation of BL therapy (days)	0.99 (0.98-1)	0.11	0.96 (0.92-0.99)	0.04
Antibiotic exposure during ICU stay prior to initiation of BL therapy	0.68 (0.41-1.15)	0.15	0.52 (0.2-1.34)	0.17
Type of initial BL therapy	0.98 (0.75-1.28)	0.88	1.17 (0.67-2.1)	0.59
Focus of infection	0.98 (0.86-1.12)	0.76	0.92 (0.73-1.17)	0.5
Severe sepsis/septic shock	1.1 (0.65-1.85)	0.72	0.38 (0.15-0.9)	0.03
Δ SOFA[a]	1.01 (0.94-1.08)	0.83	0.87 (0.79-0.97)	0.008
Microbiologically documented infection	3.96 (2.4-6.55)	<0.001	1.4 (0.62-3.15)	0.42
Presence of (non-etiologic) isolates resistant to the initial BL therapy	1.46 (0.87-2.48)	0.16	3 (1.26-7.11)	0.01

°patients with inadequate empirical therapy in microbiologically documented infections were excluded for analysis *Hosmer-Lemeshow test=1.520, *p*=0.99, ** Hosmer-Lemeshow test=3.483, *p*=0.9; ICU, intensive care unit; BL therapy, beta-lactam therapy; SOFA, Sequential Organ Failure Assessment score.
[a]ΔSOFA is SOFA score on day 0 minus SOFA score on day 2 of infection

Outcome after de‑escalation of therapy

Both de-escalation and escalation were associated with a longer antibiotic course [8 (IQR 6–10) (de-escalation) vs. 11 (IQR 8–19) (escalation) vs. 5 (IQR 4–7) (continuation) days; $p < 0.001$] and a higher total antibiotic consumption while in the ICU [12 (7–22) (de-escalation) vs. 24 (13–39) (escalation) vs. 7 (4–15) (continuation) days; $p < 0.001$]. As compared to the LOS in the ICU of patients who continued on the original therapy [continuation: 8 (IQR 5–15) days], that of patients in the de-escalation and escalation categories was significantly longer [11 (6–19) days, $p = 0.001$ and 17 (10–23) days, $p < 0.001$, respectively]. The number of antibiotic-free days on day 14 was significantly lower for patients in the de-escalation and escalation categories [1 (0–3) (de-escalation), $p = 0.04$ vs. 0 (0–1) (escalation), $p < 0.001$ vs. 2 (0–6) (continuation) days]. A subsequent infection in the ICU was more frequent following escalation of treatment than following continuation (55.3 vs. 33 %, respectively; $p = 0.008$). Neither ICU mortality nor hospital mortality differed between the three categories (Table 13).

Table 13: Patient outcome after de-escalation and escalation of anti-pseudomonal beta-lactam therapy

	Treatment				*P* value	
	Total n=344	Continuation n=221; 64%	De-escalation n=85; 25%	Escalation n=38; 11%	De-escalation vs. Cont.	Escalation vs. Cont.
Antibiotic treatment duration in the ICU for the infection under study (days)	6 [5-9]	5 [4-7]	8 [6-10]	11 [8-19]	<0.001	<0.001
Total antibiotic consumption in the ICU (days)	10 [5-20]	7 [4-15]	12 [7-22]	24 [13-39]	<0.001	<0.001
Antibiotic-free days (14 days after onset of infection) ° (n=116)	1 [0-4]	2 [0-6]	1 [0-3]	0 [0-1]	0.04	<0.001
Subsequent nosocomial infection during ICU stay (% of patients)	127 (36.9%)	73 (33.0%)	33 (38.8%)	21 (55.3%)	0.34	0.008
• Etiologic pathogen is resistant to the initial BL therapy	31/127 (24.4%)	13/73 (17.8%)	10/33 (30.3%)	8/21 (38.1%)	0.15	0.07
• Etiologic pathogen is MDR resistant	32/127 (25.2%)	15/73 (20.5%)	10/33 (30.3%)	7/21 (33.3%)	0.27	0.25
LOS in ICU following start of the infection under study (days)	9 [6-17]	8 [5-15]	11 [6-19]	17 [10-23]	0.001	<0.001
ICU mortality	76 (22.1%)	47 (21.3%)	19 (22.4%)	10 (26.3%)	0.84	0.49
Hospital mortality	117 (34%)	73 (33%)	28 (32.9%)	16 (42.1%)	0.99	0.28
Emergence of pathogens resistant to the initial BL therapy	112 (32.6%)	68 (30.8%)	29 (34.1%)	15 (39.5%)	0.57	0.29
Time interval to isolation of pathogens resistant to initial BL (n=112)	5 [3-11]	5 [4-12]	3 [2-10]	7 [3-8]	0.01	0.58
Emergence of MDR pathogens[a*]	99 (28.8%)	61 (27.6%)	24 (28.2%)	14 (36.8%)	0.91	0.25
• MRSA	5 (1.5%)	2 (0.9%)	3 (3.5%)	0	0.13	1
• VRE	3 (0.9%)	2 (0.9%)	0	1 (2.6%)	1	0.38
• *Clostridium difficile*	6 (1.7%)	5 (2.3%)	1 (1.2%)	0	1	1
• Piperacillin-tazobactam and 3rd generation cephalosporins R *Enterobacteriaceae*	28 (8.1%)	16 (7.2%)	7 (8.2%)	5 (13.2%)	0.77	0.21
• MDR Gram negative pathogens	72 (20.9%)	44 (19.9%)	17 (20%)	11 (28.9%)	0.99	0.21
▪ MDR *Enterobacteriaceae*	45	29	12	4	0.82	0.80
∟ ESBL-producing *Enterobacteriaceae*	18	15	2	1	0.17	0.48
∟ Carbapenem R *Enterobacteriaceae*	0	0	0	0	-	-
▪ MDR *Pseudomonas aeruginosa*	12	7	1	4	0.45	0.06
∟ Carbapenem R *Pseudomonas aeruginosa*	9	6	0	3	0.19	0.13
▪ MDR *Acinetobacter* spp.	1	0	0	1	-	0.15
∟ Carbapenem R *Acinetobacter* spp.	0	0	0	0	-	-
▪ *Achromobacter* spp.	2	1	1	0	0.48	1
▪ *Stenotrophomonas maltophilia*	12	7	3	2	1	0.62

ICU, intensive care unit; BL therapy, beta-lactam therapy; MDR, multidrug-resistant; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *enterococcus*; R, resistant; ESBL, extended-spectrum beta-lactamases; °in subgroup of patients with an ICU LOS ≥ 14 days after onset of infection; [a] MDR defined modified from the publication of Magiorakos et al., in accordance with the MDR definition employed by the multicenter research R-GNOSIS project[164, 165]; * patients are included once if multiple MDR pathogens are present.

Pathogens with in vitro resistance to the initial anti-pseudomonal beta-lactam antibiotic emerged in 32.6% of patients, and MDR pathogens emerged in 28.8% of patients; these values did not differ significantly when the initial beta-lactam therapy was continued, de-escalated, or escalated. The cumulative incidence estimate (CIE) of emergence of pathogens resistant to the initial beta-lactam on day 14 was 23.5% when the initial beta-lactam was continued and 30.6% when therapy was de-escalated ($p = 0.22$). The CIE of emergence of MDR pathogens on day 14 was 18.6 and 23.5% for continuation and de-escalation of therapy, respectively ($p = 0.35$). Both CIF curves are displayed in Fig. 15 a, b. Equally, subgroup analyses on microbiologically confirmed infections (ESM Fig. 15 c, d) or on only those including antibiotic courses of >5 days (ESM Fig. 15 e, f) found no differences in the CIFs of antibiotic resistance when de-escalation was compared to continuation.

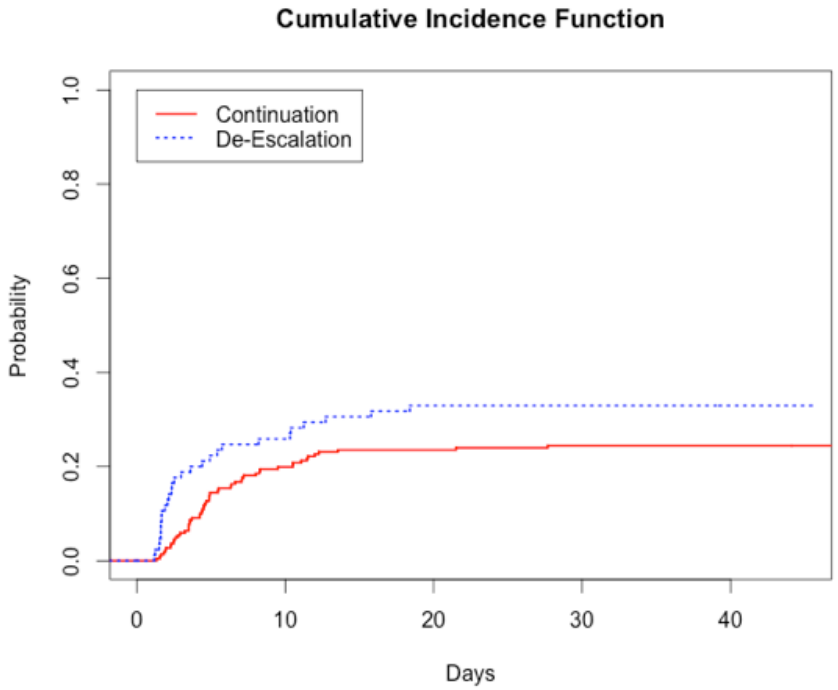


Figure 15a: Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of pathogens resistant to the initial anti-pseudomonal beta-lactam antibiotic (p=0.09, DF=1); ICU, intensive care unit

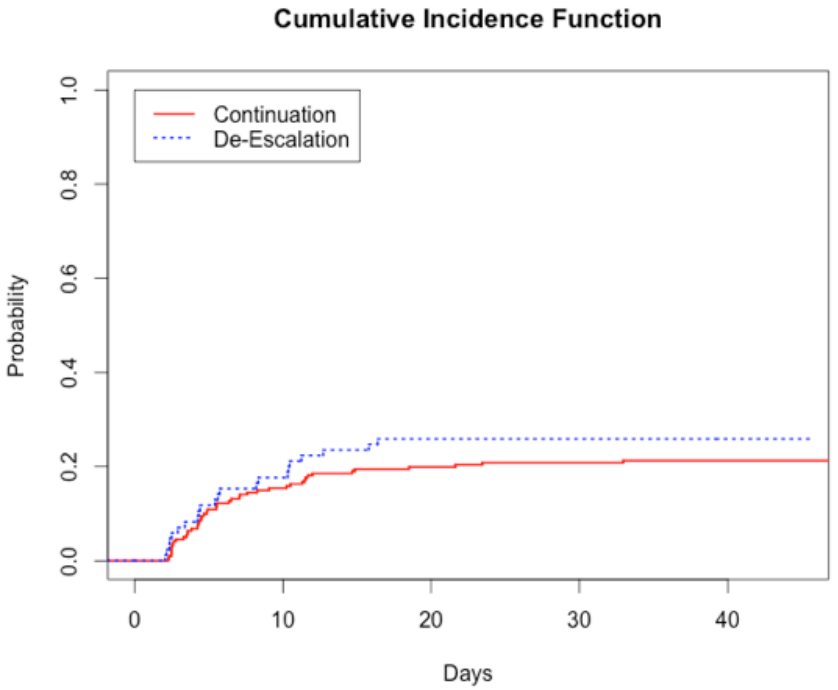
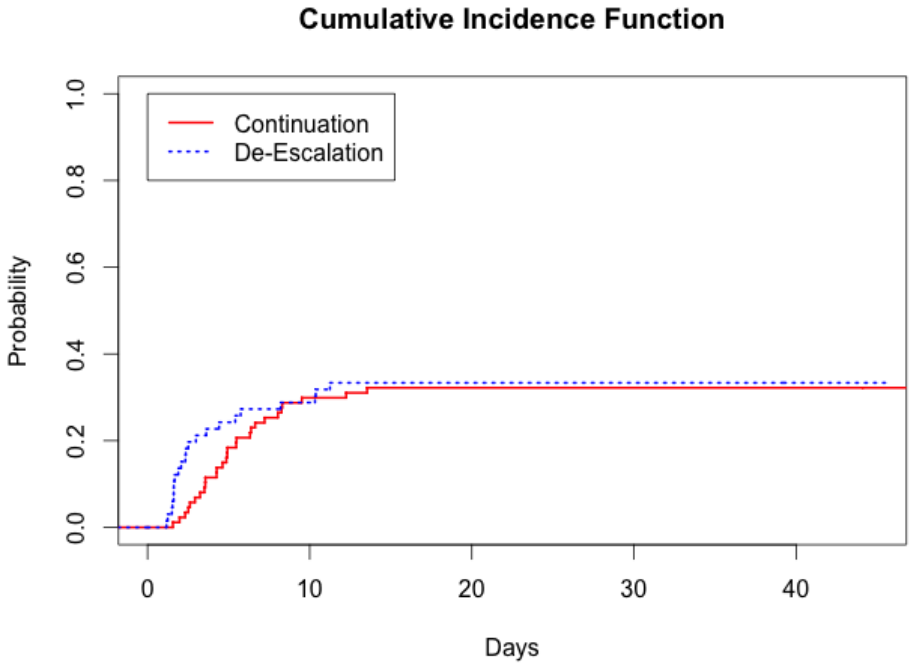
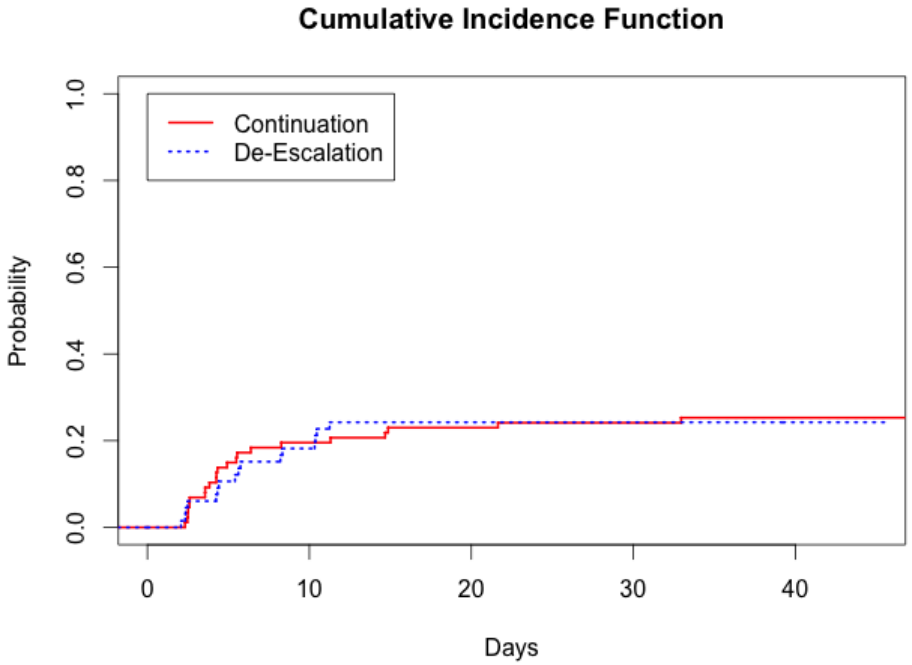


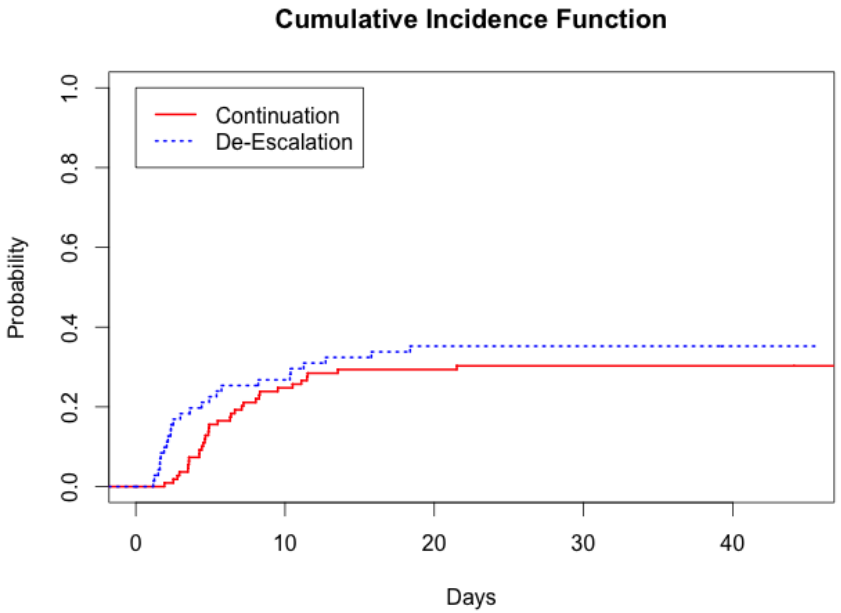
Figure 15b: Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of MDR pathogens (p=0.38, DF=1); ICU, intensive care unit; MDR, multidrug-resistant



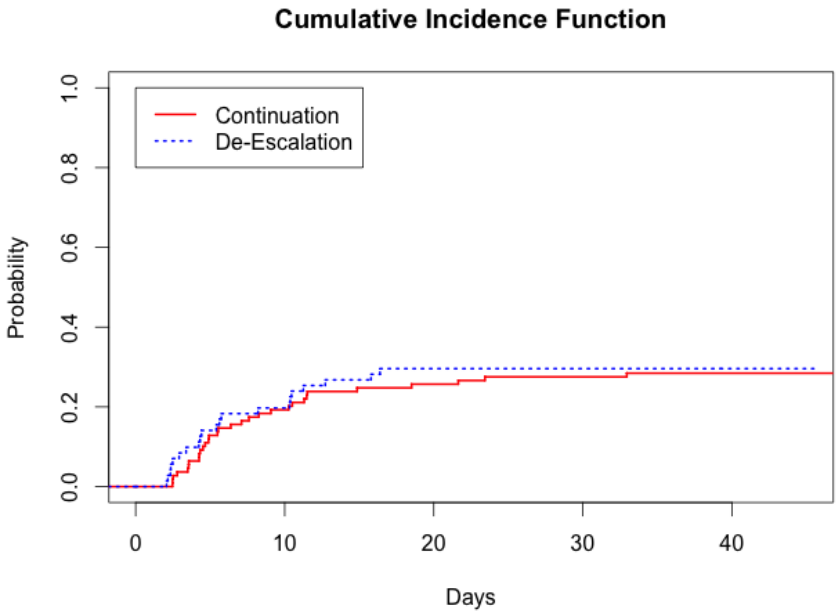
ESM figure 15c: Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of pathogens resistant to the initial anti-pseudomonal beta-lactam antibiotic in patients with microbiologically documented infections (p=0.67, DF=1); ICU, intensive care unit



ESM figure 15d: Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of MDR pathogens in patients with microbiologically documented infections (p=0.88, DF=1); ICU, intensive care unit; MDR, multidrug-resistant



ESM figure 15e: Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of pathogens resistant to the initial anti-pseudomonal beta-lactam antibiotic in patients with an ICU treatment duration > 5 days (p=0.37, DF=1); ICU, intensive care unit



ESM figure 15f: Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of MDR pathogens in patients with an ICU treatment duration > 5 days (p=0.79, DF=1); ICU, intensive care unit; MDR, multidrug-resistant

4.D.5 Discussion

To date no data have been published which confirm a beneficial effect of de-escalation on MDR emergence.[93] Previous studies that were not designed to investigate this subject were unable to demonstrate an impact of de-escalation on the selection of resistance.[95, 160, 172] Our analysis of routinely collected diagnostic and surveillance cultures is the first study to address this topic systematically. Our data show no impact of the de-escalation of empirical anti-pseudomonal beta-lactam therapy on the emergence of resistance to antibiotics.

De-escalation of anti-pseudomonal beta-lactam antibiotics was performed in one-quarter of the prescriptions, which is low in comparison with the rates reported in previous studies, ranging from 30 to 60 %.[93, 150, 157-161, 172] However, comparison between studies is hampered by the lack of a universal definition for de-escalation. Our definition of de-escalation was strict and limited to Gram-negative coverage only. Gonzalez et al. reported a de-escalation rate of 51 %, with >90% achieved by a reduction in the number of antimicrobials.[160] In contrast, the majority of de-escalations in our study resulted from substitution of the initial antibiotic by an antibiotic with a more limited spectrum [111/121 (92 %)].

Microbiological documentation of the infection has been identified as a prerequisite for de-escalation in many studies.[95, 149, 150, 158, 159, 161, 172] Although 27 % of the de-escalations in our study were for the treatment of culture-negative infections, multivariate analysis of the determinants of de-escalation found that identification of the etiologic pathogen was the single factor promoting de-escalation. However, a high number (67 %) of continued treatments for microbiologically documented infections were not de-escalated despite this being microbiologically possible, indicating that other, unresolved barriers for de-escalation may exist.[173] In contrast with prior observations we did not find an association between de-escalation and clinical improvement or less severity of the infection.[149, 157, 159, 174] Interestingly, factors associated with escalation were more complex. Escalation was significantly associated with a higher clinical severity upon presentation and unfavorable evolution under treatment, an observation which was also reported by Garnacho-Montero et al.[157] Additionally, the presence of resistant colonizing pathogens triggered the physician to escalate therapy. As the presence of resistant colonizing pathogens did not inhibit de-escalation, we suspect that during the treatment course SC are mainly used to alter the treatment in the case of severe and sustained infections. Escalation of therapy was also associated with the ICU department (surgical/medical) regardless of focus of infection, suggesting that the decision to alter the therapy may be related to more subjective characteristics or attitudes of the physician.[173]

An unexpected finding of our analysis was that the treatment duration was significantly longer in the de-escalated population ($p < 0{,}001$). To account for potential bias, we repeated this

analysis in different subgroups of patients (i.e., with the antibiotic course completed in the ICU, with etiologic pathogens identified) and calculated antibiotic-free days in the subgroup with a LOS in the ICU of ≥14 days after initiation of the infection and obtained the same result. One possible explanation is that de-escalation under the form of early antibiotic discontinuation may be hidden in the subgroup of patients who continued treatment. However, as the results are identical in different subgroups, we assume that this last reasoning cannot fully explain our observation. Alternatively, prolonged antibiotic treatment may be an unwanted side-effect of de-escalation. Although we have no firm explanation, it is tempting to propose a few potential explanations. The first is that physicians may not take the first days of empirical therapy into account when determining the full treatment duration. A second plausible explanation is the subjective perception that extending a course of a narrow-spectrum antibiotic for a few days may have fewer harmful ecological consequences than extending that of a broad-spectrum drug. The total antibiotic consumption in the ICU was also significantly higher in our de-escalated patients, but these results were mainly determined by the initial infectious episode. In contrast to our findings, Leone et al. observed an increased number of superinfections in patients following de-escalation, leading to a significantly higher total antibiotic consumption.[95] Clearly, de-escalation may itself provoke subsequent attitudes or behavior, an aspect of this study which deserves further attention.

Cumulative incidence functions were analyzed both for the emergence of pathogens resistant to the initial anti-pseudomonal beta-lactam antibiotic and for emergence of MDR pathogens, adjusting for ICU discharge and death as competing risks for the selection of resistance, and did not differ significantly between patients in the de-escalation and continuation categories. The increased emergence (although not reaching significance) of resistance in patients in the de-escalation category, as compared to those who continued the therapy, disappeared altogether when the analysis was restricted to microbiologically confirmed infections, as well as in the subgroup of antibiotic courses of >5 days; as such this increased resistance might be due to the higher number of short antibiotic exposures in the continuation group. The observation that pathogens resistant to the prescribed beta-lactam antibiotic were isolated after a median time interval of 5 days of treatment suggests that there is a widespread reservoir of resistance which rapidly results in detectable colonization even after short treatment courses. Our results find support in the study of Armand-Lefèvre et al.[21] who describe an odds ratio of 5.9 for colonization with imipenem-resistant Gram- negative bacilli in the intestinal flora of ICU patients after 1–3 days of exposure to imipenem. These findings suggest that a reduction of the number of exposures to broad-spectrum antibiotics may be a better approach to limit the emergence of resistance. An alternative hypothesis for the rapid selection of resistance is derived from

simulation studies that demonstrate a lower probability to achieve adequate pharmacokinetic/pharmacodynamic targets for more narrow-spectrum agents.[175]

De-escalation on the second or third day of therapy is recommended.[90, 91, 156] In our study we de-escalated therapy after a median treatment duration of 3 (IQR 3–5) days, which is in accordance with previous reports.[95, 160, 172] As physicians rely on microbiology results for their decision to de-escalate, it seems almost impossible to narrow this time-frame due to the limitations of current microbiology practices.

Our study has a number of limitations. First, it is a retrospective study, although all antibiotic-related data were recorded prospectively. Second, our study is monocentric in a setting with relatively low resistance levels, and the impact of de-escalation may be different in other ecologies. Third, our ranking system of incremental Gram-negative antimicrobial activity is only one of many possible approaches. In previous papers focusing on the subject, ranking of antimicrobials by their spectrum of activity has proven to be difficult, resulting in conflicting definitions.[176, 177] Moreover, most prior observational studies do not provide the ranking of the treatments that was used, which makes interpretation and comparison difficult.[157, 160, 161, 172] Fourth, we lack information regarding the antibiotic exposition prior to ICU admission. However, keeping in mind that in the univariate analysis de-escalated patients had significantly shorter hospitalization duration before the initiation of the beta-lactam treatment and significantly less previous antibiotic exposure in the ICU, it is unlikely that prior antimicrobial consumption was higher in the de-escalated population. Finally, it is reasonable that different de-escalation strategies are not comparable with respect to patient outcome and impact on microbial ecology.

In conclusion, in our study population, de-escalation of anti-pseudomonal beta-lactam antibiotics, as performed by the replacement of antibiotic treatment by a more narrow-spectrum agent, was mainly driven by the presence of etiologic cultures. We did not observe a beneficial effect of de-escalation on the emergence of resistance. Consequently, we conclude that de-escalation should not be considered to be a safe strategy underpinning the unlimited empirical use of broad-spectrum therapy. Our results confirm the urgent need for a uniform definition on de-escalation and for future randomized controlled trials to determine the most optimal de-escalation strategy and, by extension, the most optimal antibiotic strategy for reducing overall antibiotic exposure and antimicrobial selection pressure.

Authors' contributions

LDB and PD conceived the study, participated in its design and coordination, analyzed the data, and drafted the manuscript; WD, JC, LDB, KV, and BG performed data acquisition and analyses; WD, JC, BG, KV, JB, GC, JDW, and JD critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgments

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Compliance with ethical standards

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Take-home message:

The results of this study do not confirm the expected favorable effect of de-escalation of anti-pseudomonal beta-lactam antibiotic treatment on the selection of antimicrobial resistance. De-escalation should therefore not be considered to be a safe strategy underpinning an unlimited empirical use of broad-spectrum combination therapy. Future research to determine the most optimal de-escalation strategy and by extension the most optimal antibiotic strategy reducing overall antibiotic exposure and antimicrobial selection pressure is essential.

E. LINKING ANTIBIOTIC, MICROBIOLOGY AND CLINICAL DATA THROUGH AN ELECTRONIC PLATFORM ENABLES IDENTIFICATION OF ANTIMICROBIAL STEWARDSHIP TARGETS: A PROOF-OF-CONCEPT STUDY

Liesbet De Bus, Bram Gadeyne, Jerina Boelens, Geert Claeys, Dominique Benoit, Johan Decruyenaere and Pieter Depuydt

Submitted

4.E.1 Abstract

Longitudinal surveillance of infection treatment facilitates identification and prioritization of stewardship interventions. Antibiotic prescription in patients admitted to the Intensive Care Unit of Ghent University Hospital (January 1st 2013 - December 31st 2016), was merged with microbiology and clinical data during clinical workflow through a designated software program. Prolonged courses (>3 days of therapy) of glycopeptides, oxazolidinones and carbapenems that were potentially unjustifiable by previously defined criteria were identified. Thirteen percent of glycopeptide/oxazolidinone versus 33 % of carbapenem consumption was classified as potentially unjustified. Linking of antibiotic, microbiology and clinical data during daily routine may facilitate targeting of stewardship interventions.

4.E.2 Introduction

The need for a well-designed antibiotic stewardship program (ASP) is universally recognized, especially in the intensive care unit (ICU) which is a hotspot for antibiotic use.[2, 3] As healthcare resources have to be used judiciously, potential stewardship intervention targets have to be weighed carefully.[122] The computerization of the patient chart has offered the potential to record healthcare processes, including antibiotic treatment, as complete data of high resolution in a way that minimally interferes with the healthcare deliver's workflow.[102]

In the ICU of Ghent University Hospital, a locally developed software program automatically integrates all infection related data from distributed stand-alone vendor specific systems. A concise overview is presented to the physician in a graphical form for each ICU patient. As such, this software facilitates manual linking of antimicrobial prescription data, microbiology data and clinical information during daily routine.[102] The aim of the current study is to illustrate the potential of this longitudinal surveillance strategy to target possible stewardship interventions through an example case assessing antimicrobial overuse.

4.E.3 Materials and methods

Setting

This study was conducted from January 1st 2013 until December 31st 2016 at the medical and surgical (36 beds) ICU of Ghent University Hospital (1054 beds). The hospital Ethics Committee approved the study (registration number B670201628197) and waived informed consent based on the non-interventional nature of this study. Patients aged 16 years or older were included.

Patients are managed in a closed ICU. Antibiotic prescriptions are at the discretion of the attending ICU physician, without the use of stringent protocols or antibiotic restrictions. Interdisciplinary staff meetings take place on a regular basis. Treatment duration and opportunities for de-escalation are evaluated daily.

An Intensive Care Information System (Centricity Critical Care, GE Health Care) integrating physician order entry, medication administration recording and patient monitoring data is available bedside. A software program, COSARA (Computer-based Surveillance, Alerting of infections, antimicrobial Resistance and Antibiotic consumption in the ICU) was developed by a consortium of the Ghent University Hospital ICU department and the Department of Information Technology (INTEC) of the Faculty of Engineering of Ghent University.[102] COSARA automatically integrates infection related data from different electronic data sources and presents these as a

graphic overview (Supplemental Digital Content 1). The antibiotic prescription is presented as a horizontal bar running along a timeline (antibiotic bar). This bar is accompanied by a second bar describing the indication for this antibiotic (infection bar). A preliminary version of the infection bar is fed by data from a questionnaire that 'pops up' in real-time after any antibiotic prescription and inquires the prescriber about indication, severity, focus and probability of infection and presence of microbiological data guiding the antibiotic choice. This preliminary bar can be altered when more data concerning the origin and clinical evolution of the infection become available. In addition, the coupled antibiotic-infection bars can be linked to microbiological culture results. All preliminary infection bars were reviewed and modified if necessary by the investigators LDB and PD after consultation of the ICU physician or the patient charts.

Drill-through-to-detail analysis of antimicrobial use

In accordance with the recommendations of the Centers for Disease Control and Prevention (CDC), days of therapy (DOT) was defined as the number of days with systemic administration of at least one dose of an antimicrobial agent as recorded by COSARA.[36] We focused on three 'last-resort' antibiotics for which a restricted use is recommended: carbapenems, glycopeptides and oxazolidinones.[20, 178, 179] We combined utilization data with clinical and microbiology info by drill-through-to-detail analysis of our database (figure 16). To demonstrate the flexibility of our dataset we focused on the identification of unjustified sustained treatment courses. We assumed that prolonged (> 3 DOT) use would be potentially unjustified in one of the following conditions: (1) prolonged prophylactic therapy, (2) prolonged therapy in low probability infections, (3) prolonged empirical therapy (negative diagnostic cultures) in moderate/high probability infections and (4) prolonged broad-spectrum therapy in microbiologically confirmed infections when de-escalation is possible based on susceptibility results of causative pathogens.

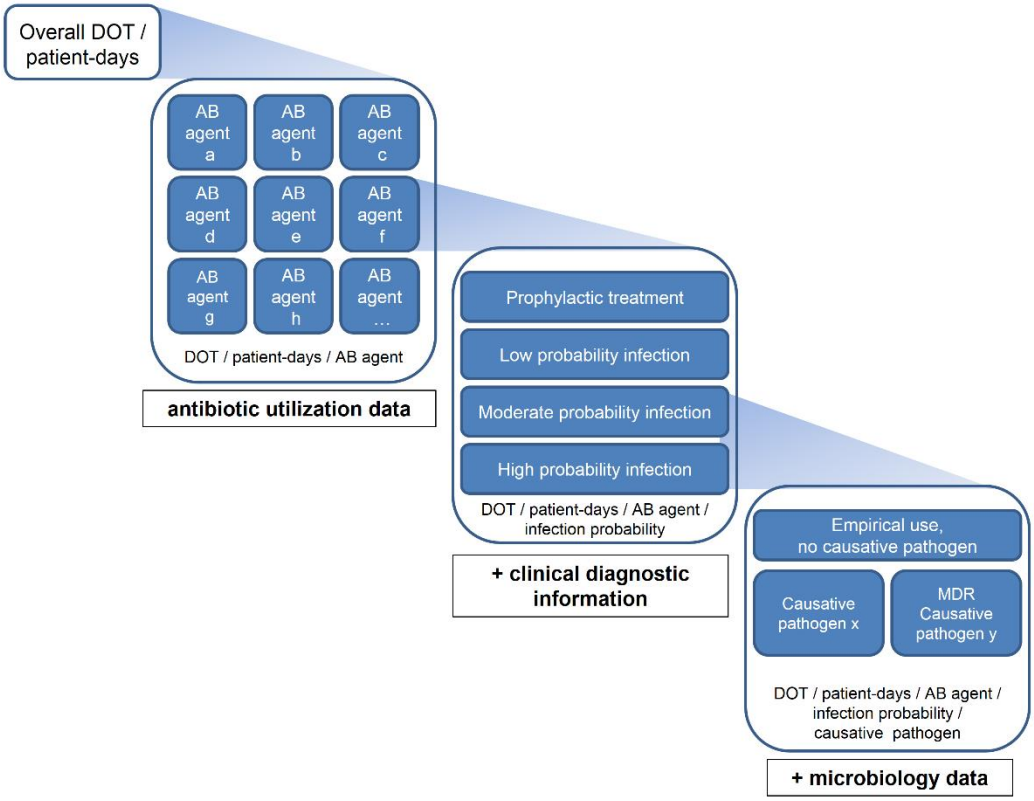

Figure 16: Drill-through-to-detail analysis of antimicrobial use

4.E.4 Results

A total of 10743 ICU admissions were recorded in 8763 patients resulting in a total of 47403 patient days from January 1st 2013 until December 31st 2016. ICU and hospital mortality was 10.7% (n=936) and 15% (n=1314) respectively. Median APACHE II score at admission was 18 (IQR 13-25). Methicillin resistance was present in 23% of the *Staphylococcus aureus* isolates in our ICU population. Vancomycin resistance was present in 1.9% of the *Enterococcus* species isolates. Extended spectrum beta-lactamase production (ESBL) was present in 33% of *Enterobacteriaceae* isolates, whereas carbapenemase production was present in 1.2%.

A total of 14908 antibiotic courses were administered, resulting in 58413 DOT (1232 DOT/1000 patient days). Overall consumption of carbapenems, glycopeptides and oxazolidinones was respectively, 94.7, 62.6 and 37.6 DOT/1000 patient days. All three antibiotic classes were principally used to treat high probability infections. Thirty-three percent of the carbapenem consumption and 13 % of the combined glycopeptides and oxazolidinones use was identified as potentially unjustified. A detailed overview is provided in table 14.

Type of potentially unjustified antibiotic use	Carbapenem	Glycopeptides + Oxazolidinones
	n DOT in excess (% of total DOT/ class)	n DOT in excess (% of total DOT/ class)
Type 1: Prolonged prophylactic therapy	**12 (0.3%)**	**32 (0.7%)**
Type 2: Prolonged therapy in low probability infections	**66 (1.5%)**	**52 (1.1%)**
Abdominal infection	5	26
Catheter related infection	-	3
Neutropenic fever	7	1
Respiratory infection	28	1
Other infection focus	2	5
Unknown infection focus	24	16
Type 3: Prolonged empirical therapy in moderate/high probability infections without positive diagnostic cultures	**691 (15.4%)**	**369 (7.8%)**
Abdominal infection	347	165
Catheter related infection	2	14
Neutropenic fever	28	12
Respiratory infection	169	65
Skin & soft tissue infection	21	27
Uro-genital infection	4	3
Other infection type	16	22
Unknown infection focus	104	61
Type 4: Prolonged broad-spectrum therapy in microbiologically confirmed moderate/high probability infections when de-escalation is possible	**721 (16.1%)**	**146 (3.1%)**
Abdominal infection	309	58
Catheter related infection	9	1
Neutropenic fever	14	-
Respiratory infection	140	25
Skin & soft tissue infection	28	10
Uro-genital infection	9	-
Other infection type	25	28
Multiple infection foci	144	7
Unknown infection focus	43	17
Total of unjustified antibiotic use (% of total DOT/antibiotic class)	**1490 (33.2%)**	**599 (12.6%)**

Table 14: Potentially unjustified antibiotic use

4.E.5 Discussion

In this manuscript we demonstrate the added value of a detailed database which is built up by continuously linking antimicrobial prescription data, microbiology data and clinical diagnostic information of ICU patients during clinical workflow to support antibiotic stewardship decision-making.

A detailed insight in the aspects driving antimicrobial use is desirable to support the selection of potential stewardship targets.[122] In this study we focused on carbapenems and glycopeptides/oxazolidinones as 'last resort drugs'. Consumption figures of the same magnitude were observed during a 4-year period. Supplementing these data with microbiology and clinical info to identify potentially unjustified sustained antibiotic courses learned that 33 % of the carbapenem DOT/patient-days was deemed to be redundant, as compared to only 13 % of the glycopeptides/oxazolidinones utilization. Based on these results an intervention targeting carbapenem overuse seems to take priority over handling glycopeptides/oxazolidinones overconsumption in our institution. Accurately combined information on three different aspects of an individual treatment course (antibiotic prescription, infection diagnosis and microbiology) was mandatory to come to this conclusion.

Continuous merging of infection related data which is elementary for our surveillance strategy may seem insurmountable due to personnel and time restraints. Over the last years, ICU staff members integrated this process in their workflow by the use of COSARA.[102, 124] Two basic principles underlie our registration. First, we map the motivation for each electronic antibiotic prescription through a questionnaire at the point of care. Second, COSARA presents all information on infection in a concise, visually attractive and user-friendly format which promotes incorporation of the merging process in clinical tasks.

Our study has limitations. First, computerized physician order entry is crucial to implement this stewardship proposal, but at the same time the persistent commitment of dedicated physicians is vital for its chances of success. Integrating the linking in daily routine, real-time presentation of this information during ward rounds and staff meetings and employment of the collected data for computerized decision support are ways to increase its sustainability. Second, the value of all surveillance systems depends largely on the quality of the data that is incorporated. A previous analysis assessing the validity of the diagnostic information recorded in COSARA compared to conventional surveillance data showed good agreement between both methods.[124] Bearing these first two limitations in mind, a multicenter application of our system will be needed to assess its general applicability. Finally, we have to acknowledge that successful implementation of a stewardship intervention is not guaranteed solely by the identification of an area of potential antibiotic overuse. Although an early evaluation of ongoing antibiotic treatment need ('antibiotic

time out') is recommended by the CDC, many barriers may withhold a physician to act upon a recommendation for discontinuation.[36, 180] Future interventions at the point of care are required to evaluate and refine our strategy.

Conclusion

Continuously connecting antimicrobial prescription data, microbiology data and diagnostic information during workflow leads to the build-up of a comprehensive dataset which may facilitate internal stewardship decision-making.

Acknowledgements

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5 DISCUSSION

The key objective of this PhD project was twofold. On the one hand, we evaluated the feasibility and validity of our locally designed software program, COSARA, to assist in surveillance. On the other hand, based on the information that was captured through the use of COSARA, we aimed to acquire more insight in our local antibiotic prescription practices and microbiological resistance patterns to support the design of an ASP.

A. USE OF A COMPUTER-ASSISTED REGISTRATION PROGRAM TO FACILITATE SURVEILLANCE IN THE ICU

Confronted by clinical problems during daily workflow as ICU physicians, we sought to develop and design a software program assisting in everyday infection management. The time-consuming process of collecting a patient's data in case of a complex history of infection was an important incentive for the development of a clinical data visualization dashboard. The absence of easy accessible and detailed information on antibiotic utilization in the ICU emphasized the need for the construction of a registration tool. For this purpose, multidisciplinary discussions harmonizing the aspirations of ICU personnel with IT possibilities were held, which finally resulted in the build-up of the COSARA software.

COSARA is situated among a wide variety of existing electronic or automated surveillance tools but has many particularities. As mentioned previously, patient and infection related data are assembled through the software and presented in a graphical format to the user. This information needs to be supplemented with clinical information which is introduced by physicians: a) a pop-up questionnaire at the moment of antibiotic prescription and b) a reassessment and fine-tuning of these pop-up data during the course of the treatment. Subsequently, COSARA is an indispensable facilitator of the surveillance process, but at the same time, a substantial amount of manual input is required. As such, COSARA has to be categorized as a semi-automated ESS.

As explained before, clinical information has proven to be a valuable data source in the context of surveillance.[46, 49] This is not unsurprising as clinical signs and symptoms are a crucial component in the majority of traditional surveillance definitions. Most fully automated ESS struggle with the collection of clinical information from EHRs and as a rule this information is not available in a structured format. In a study on SSI surveillance, however, highly sensitive and specific results were obtained by the investigators through the mandatory reporting of

structured clinical data.[181] When linking a diagnosis to an antibiotic prescription in COSARA, physicians are asked to select an infection from a predefined limited list which leads to the build-up of a structured dataset. No specific rules or definitions are followed during this process. A subsequent assessment of infection probability is asked for each treatment course as antibiotics are commonly prescribed for prophylactic reasons or in patients with a low suspicion of infection. Our approach differs significantly from traditional surveillance following formal checklists and criteria, therefore a comparison of both strategies was deemed essential. Surveillance through COSARA was compared with PBS for three infection types: BSI, RTI and UTI.[124] Good agreement, reflected by an overall kappa score of 0.74 was recorded. Not unexpectedly, inter-observer variability was the major reason for disagreement between CAS and PBS, which is inherent to the use of different diagnostic criteria by both surveillance methods. Test characteristics of CAS through COSARA fall within the range of the results reported in other studies on electronic surveillance; high sensitivity (72-100%) and diverging specificity (37-100%) results for BSI, comparable figures for UTI (sensitivity and specificity of respectively 86-100% and 59-100%) and RTI (sensitivity and specificity of respectively 71-99% and 61-100%).[37] Importantly, due to time and personnel restraints which limited PBS, the validity of COSARA as surveillance tool was only evaluated for these 3 selected infection types.

COSARA, as it is currently in use in our ICU, aims to integrate surveillance in the daily workflow of the ICU physician. Collecting structured clinical information without adhering to strict diagnostic criteria was a well-considered decision to ensure practical feasibility of sustained data collection. Redefining the preliminary infection diagnosis and linking of microbiology results to an antibiotic-infection combination can be done by each physician involved in patient care and requires only a minimal effort. Over the last few years however, we decided to appoint designated COSARA users in our ICU that devote extra time to the reassessment of infection diagnoses and linking of microbiological information; a trade-off that has been made to guarantee completeness and consistency of data collection. The design of COSARA, however, permits less or more standardized surveillance approaches. For instance, dedicated surveillance personnel may be assigned to perform surveillance, supported by COSARA, using traditional international definitions. Alternatively, additional objective criteria can be paired with the captured clinical infection diagnoses to increase specificity of our surveillance system (see below). Performance and time expenditure need to be reevaluated if one should decide to employ COSARA in this alternative manner.

Semi-automated ESS require a persistent commitment of both the prescribing physician and the dedicated COSARA user to ensure registration of correct clinical diagnostic information. We observed that completion of the pop-up questionnaires, although this takes less than one

minute, is sometimes performed incorrectly. We hypothesize that this is mainly the result of an incomplete understanding of the antibiotic decision-making process by physicians in training or the fact that some physicians consider this act to be of minor importance in the treatment process of their patient. Semi-automated systems are inherently subject to the pitfalls of traditional manual surveillance i.e. human error, inter-observer variability and incomplete data capture. As a result COSARA seems less fit for benchmarking purposes compared to fully automated ESS. The use of additional filters when querying the COSARA database may partially overcome this problem. In the case of VAP for instance, worsening of oxygenation, presence of fever or hypothermia and the isolation of a respiratory pathogen 48 h before or after the initiation of a new antimicrobial treatment are all objective and easy accessible data. The clinical diagnosis which is stored in the COSARA database can be matched to these objective criteria and as such the specificity of our surveillance approach may be increased.

Identification of an infection by COSARA is triggered by the initiation of antibiotic treatment. A CLABSI which is simply treated by catheter removal or an infection which is untreated in the setting of therapeutic restrictions, is thus not captured by means of COSARA. On the other hand, each and every electronic antibiotic prescription has a diagnostic label assigned to it. The resulting global overview on antimicrobial consumption is unique in its kind. One of the incentives for the continuing development of ESS over the last decade, is the fact that manual surveillance is often limited to specific conditions or pathogens due to time and personnel restraints. Unfortunately, the number of ESS that covers a wide range of infections or treatments is still limited. Only one study, performed in a tertiary care teaching hospital in Finland, reported on a continuous hospital-wide surveillance system covering all infection types.[52] Similarly to COSARA, the described system required manual input by the treating physician and dedicated surveillance personnel, case finding was treatment-based and performance of the system was only tested for a subset of infection types. An additional limitation of most ESS is made up by their dichotomous classification methods. Detection of 'borderline' infections is hampered by their design. MONI-ICU, an ESS using fuzzy set theory and fuzzy logic, has gained experience with non-dichotomous infection surveillance.[58] A significant number of borderline infections (or clinical suspicion of infection) was detected by this system, particularly when clinical information was incorporated in the algorithm. The authors state that their findings reflect the diagnostic difficulties of ICU physicians. Although this aspect is not touched in the article, it would be interesting to know in how many of these cases antibiotics were initiated. COSARA records information on infection probability. Identification of low and intermediate probability infections is just as important as registration of definite infections as these borderline cases comprise an important target for ASP. This was clearly illustrated in the four-year descriptive

analysis of antibiotic use in our ICU and will be discussed further in the second part of this discussion.

Performance standards of ESS are largely determined by their data access time which has to be held as short as possible.[68] A distinct COSARA module allows real-time autonomous execution of a wide range of predefined analyses. Additional data extraction from the COSARA database can be performed within limited time frames but requires the assistance of an IT specialist. The architecture of the database, on the other hand, allows physicians to address complex research questions through flexible merging of these raw COSARA data.

The validity of COSARA as surveillance tool may differ between different ICU settings. The COSARA software has been deployed in a second university hospital ICU (Antwerp University Hospital). Software implementation was not hindered by the fact that both hospitals use an ICIS from a different manufacturer. Until now, further information on performance status and clinical implication of COSARA is unavailable for this center. Theoretically, the basic requirements for the implementation of the software merely consist of the use of CPOE for antibiotic prescription and accessibility of microbiology results in an electronic format. However, we need to stress once more that data quality and consistency depends largely on the input of accurate clinical information. The level of data fine-tuning and data control will determine the performance level of our ESS and its usefulness in patient care. As mentioned before, validity and time expenditure of COSARA as surveillance tool need to be reassessed if it is deployed in a different ICU setting.

Advantages and limitations of the current COSARA concept as a surveillance tool are summarized in table 15.

Advantages and disadvantages of COSARA as surveillance tool
Advantages
▪ Use of a data visualization dashboard to promote information management and manual linking of antibiotic, clinical diagnostic and microbiology data
▪ Surveillance is not limited to a selected subgroup of antibiotics or infections o Possibility to generate a global overview of antibiotic use o Non-dichotomous assessment of the presence of infection (captures spectrum of infection probability: low-intermediate-high)
▪ Captures nuances, complex diagnostic info and clinical judgement
▪ Allows to capture many-to-many relationships between antibiotics, infection diagnoses and microbiology (e.g. one infection can be treated by multiple antibiotics, one antibiotic can be used to treat multiple infections)
▪ Information is stored as structured data
▪ Easy and timely access to data warehouse
Disadvantages
▪ Substantial amount of manual input required o Dedication of physicians / healthcare personnel is mandatory o Subject to interrater variability and human error
▪ Less suited as benchmarking tool
▪ Infections not treated with antibiotics are not captured

Table 15: Advantages and disadvantages of COSARA as surveillance tool

B. INVESTIGATION OF ANTIBIOTIC PRESCRIPTION AND ANTIBIOTIC RESISTANCE IN THE ICU TO SUPPORT THE DESIGN OF AN ASP

COSARA is designed to support infection management in our ICU and ultimately, improve bedside patient care. The potential of COSARA as facilitator of antibiotic stewardship was clearly demonstrated throughout this PhD project by its ability to construct large longitudinal datasets on infection. As explained above, hospital ASP truly rely on monitoring for the identification of potential stewardship intervention targets and the subsequent evaluation of a stewardship action (figure 1).[36] A descriptive analysis of a dataset covering four years of surveillance was performed to get a bird's eye view of local antibiotic prescribing practices. Subsequently, we selected 3 ASP interventions that are recommended by the CDC for further exploration in our ICU. These general recommendations were reformulated to more specific ASP targets which were considered to be clinically relevant in our setting (table 16). Clear outcome measures for the selected antibiotic stewardship actions were defined and subsequently assessed by the use of COSARA. The results of these analyses enabled us to calculate presumed or actual impact of these stewardship actions. Until now, we have used this information mostly for research purposes and actual stewardship actions were not yet linked to our data. The next level of stewardship, active interference in the clinical workflow based on the aforementioned evaluations, falls out of the scope of this PhD project, and will be touched in the future perspectives section.

ASP interventions recommended by CDC	Evaluation of targeted ASP interventions in Ghent University Hospital ICU	Outcome measures extracted by means of COSARA
Develop facility-specific treatment recommendations based on national guidelines and local susceptibility data	Evaluation of: a) current empirical AB prescription in HAP b) added value of a facility-specific treatment guideline for empirical AB prescription in HAP c) added value of the incorporation of SC results in a facility-specific treatment guideline for empirical AB prescription in HAP	a) Appropriate antibiotic coverage rate b) Consumption of broad-spectrum antibiotic agents
Evaluate the possibility of using a more targeted antibiotic to treat an infection (de-escalation)	Evaluation of: a) determinants of de-escalation and escalation of empirical beta-lactam AB prescription b) the effect of de-escalation on patient outcome	a) AB treatment duration / AB-free days b) Nosocomial infection c) Length of stay d) Mortality e) Emergence of antibiotic resistance
Reassess the continuing need and choice of antibiotics 48 hours after antibiotics are initiated (antibiotic 'time-out')	Evaluation of prolonged courses of glycopeptides, oxazolidinones and carbapenems	Percentage of glycopeptide, oxazolidinone and carbapenem courses that is potentially unjustifiable

Table 16: Summarizing overview of antibiotic stewardship program interventions that were explored

ASP: antibiotic stewardship program; CDC: Centers for Disease Control and Prevention; ICU: intensive care unit; AB: antibiotic; HAP: hospital-acquired pneumonia; SC: surveillance culture

5.B.1 A complete and multifaceted overview of antibiotic use and infection diagnosis in the ICU

Evaluation of antibiotic prescription in our ICU during a four-year period, revealed that consumption figures were high: 1232 DOT/1000 patient days; two-thirds of all ICU patients were exposed to at least one antibiotic class; one-third of patients with an ICU length of stay (LOS) of 48 h or more, were exposed to three or more antibiotic classes. The majority of studies on antibiotic use and infection diagnosis focus on a specific targeted antibiotic class or infection type. As a rule, a lot of attention is given to infections that are ICU-acquired, as these infections are considered to be (at least partially) preventable. In our setting, however, an infection was diagnosed within the first 48 h of admission in 54% of patients with an ICU LOS of 48 h or more. In general, these infections are considered to be acquired in the community or the hospital and as such they cannot be prevented by optimization of ICU care. On the other hand, we observed that a significant amount of our antibiotic consumption is used to treat infections with a moderate to low probability, and antibiotics were often started on an empirical basis in order not to miss a potentially treatable condition in an unstable patient. In order to reduce antibiotic exposure in this context, interventions in our ICU will need to focus more on enhancing diagnostic accuracy prior to the start of antibiotics and on the antibiotic trajectory following its initiation. As long as the use of rapid diagnostic tools is in its infancy, restricting antibiotic use 'upstream' , however, will remain more challenging compared to 'downstream' restriction at a time when more diagnostic information becomes available. A systematic reevaluation of ongoing treatment need and duration, 48-72 h following the initiation of a treatment ('antibiotic time out'), could thus serve as a meaningful stewardship action.[35, 182] A more detailed calculation of the antibiotic sparing potential of this strategy was conducted for 3 selected antibiotic classes: carbapenems, glycopeptides and oxazolidinones (see below).

Quite surprisingly, prophylactic treatment accounted for 25% of the overall antibiotic consumption. As guidelines on non-perioperative prophylaxis, e.g. prophylaxis following trauma or aspiration are not available in our ICU, we feel that implementation of guidelines on this matter may lead to a significant reduction in antibacterial use. As regards the antifungals, clear recommendations on the prophylactic use of azoles will probably significantly restrain its overall consumption.

The unique intuitive approach of categorizing infections by its probability was once more stressed as an important prerequisite to permit data collection on global antibiotic consumption over prolonged periods of time. Although this strategy may complicate comparison between different centers, the detailed insight in overall antibiotic use is of inestimable value in the construction of an ASP. In addition, when required, inter-institution evaluation may be improved

by the additional use of a set of objective criteria such as laboratory and microbiology results and radiology reports when assessing specific types of infections.

5.B.2 Empirical antibiotic prescription in hospital-acquired pneumonia and the added value of the use of surveillance cultures

Analysis of 113 episodes of HAP, acquired in our ICU in the period between November 1st 2010 and October 31st 2012, learned that causative pathogens were mainly Gram-negative (84%). Clinical risk factors for the involvement of MDR pathogens were present in 87.6% of HAP episodes. These finding are not surprising given the complex history of our patients with frequent prior hospitalization and antibiotic exposure. It emphasizes however, that the choice of an adequate antibiotic treatment is challenging in the absence of diagnostic culture results. Over the last few years, the use of systematic SC was incorporated into our clinical workflow, aiming to predict involvement of MDR pathogens and to guide empirical antibiotic choice.[87]

As outlined before, our study evaluated the potential of a formal treatment algorithm based on local ecology data in our ICU (LEBA). Furthermore, we assessed the added value of incorporating SC results in such an algorithm (SCBA). We pursued at least 85% appropriate coverage rate when constructing both algorithms. While this number is somewhat arbitrarily, we aimed to set a rate which is in the highest range of what is practically achievable yet avoids non-discriminative combination therapy. There is increasing appreciation of the fact that aiming for maximal coverage rates may no longer be justified if this is at the expense of inducing further resistance and jeopardizing our future empirical treatment possibilities.[183] At our center, maximal appropriate coverage rates would only be possible with the non-discriminative use of aminoglycoside combination schemes: apart from ecological issues, this may not lead to better patient outcome.[184]

LEBA and SCBA were retrospectively applied on the cohort of 113 HAP episodes. Appropriate antibiotic coverage rate did not differ significantly between the actual prescribed treatment (84.1%), the antimicrobial choices that were proposed by LEBA (88.5%) and those suggested by SCBA (87.6%). In other words, it is unlikely that appropriateness of empirical treatment will be influenced by the implementation of the proposed treatment algorithms. However, major differences were seen when evaluating the spectrum of the administered or proposed treatment schemes. LEBA suggested to use significantly more combination therapy and carbapenems compared to SCBA. Eliminating the use of aminoglycosides and glycopeptides in the LEBA would lead to a reduction in appropriate coverage rate from 88.5% to 81.4% (p=0.008) (unpublished results). The actual prescription of combination therapy and carbapenems on the other hand did

not significantly differ from the use that was proposed by SCBA (respectively, 13.3% versus 7.1% (p=0.12) and 15.9% versus 21.2% (p=0.35)) (unpublished results). SCBA does not recommend the use of combination therapy, unless this is motivated by the presence of MDR pathogens in the SC results. These results suggest that physicians in our ICU already rely upon the high negative predictive value of SC and withhold broad-spectrum therapy in the absence of MDR.

As compared to actually prescribed treatment, strict adherence to SCBA would reduce administration of broad-spectrum therapy even more. It is important, however, to recognize that the scale we constructed to quantify the spectrum of the antibiotic treatment is artificial. Until now, there is no general consensus on the spectrum and resistance promoting potential of individual antibiotic regimens nor on combinations thereof. We ranked combination therapy and carbapenems respectively highest and second highest, in accordance with the prevailing opinion in the current literature.[176, 177] Ranking of the remaining antibiotic agents proved to be more challenging. Our ranking of beta-lactam antibiotics is in line with the consensus definition of an international expert panel.[177] The position of fluoroquinolones on the other hand may be challenged. As fluoroquinolone treatment comprised only 10% of empirical antibiotic choices, altering its position on the scale will probably not affect main study results.

To definitively confirm or refute whether the implementation of an empirical antibiotic algorithm would have benefit in terms of appropriate coverage and antibiotic consumption, a prospective study is needed. Barriers and facilitators of a physician's adherence to the algorithm will need to be assessed as these will influence performance status of the algorithm. The future role of COSARA as an active computerized clinical decision support system (CDSS) interfering with empirical antibiotic decision-making at the point of care, provides another intriguing new field of research (see future perspectives).

5.B.3 Local antibiotic de-escalation practices and impact on the emergence of antibiotic resistance

De-escalation is an appealing antibiotic stewardship strategy as it permits the empirical use of broad-spectrum agents up until the moment that more clinical, diagnostic and microbiological information becomes available. For years, de-escalation has been widely promoted in our ICU. The possibility to de-escalate an empirical treatment is evaluated and encouraged on daily ward rounds and during multidisciplinary discussions with clinical microbiologists and infectious diseases specialists. Publication of the first multicenter randomized non-inferiority trial in 2014 by Leone et al., comparing de-escalation with continuation of therapy triggered a discussion

(that is still ongoing) regarding the safety of this strategy.[95] Unexpectedly, de-escalation was inferior to continuation of treatment in terms of ICU LOS. Additionally, de-escalation was associated with an increased number of superinfections in this non-blinded trial. This study was not designed to evaluate the effect on microbiological selection pressure. As the ecological impact of de-escalation was a largely unexplored domain, we decided to assess the emergence of antibiotic resistance following de-escalation through analysis of the COSARA dataset combined with routine SC results. The results of our trial, including longer treatment durations in de-escalated patients and no impact of de-escalation on emergence of antibiotic resistance, were unforeseen and added to the vivid discussion that was initiated earlier.

As for all studies on de-escalation, our results need to be evaluated in the light of the definitions that were used. A ranking system of antibiotic agents by increasing order of Gram-negative spectrum was created and a movement down on this scale was perceived as antibiotic de-escalation. De-escalation was performed in only 25% of anti-pseudomonal beta-lactam antibiotic prescriptions, consisted mainly of replacement of one antibiotic by another with a smaller spectrum and was significantly associated with the identification of an etiological pathogen. However, based on the susceptibility data of the presumed etiologic pathogen, 67% of continued treatments for microbiologically documented infections could have been de-escalated according to our ranking system. Clinical appreciation may have influenced the subjective decision whether or not to de-escalate. To identify these barriers for de-escalation, however, one would need a prospective study with interviewing.

Both emergence of resistance to the initial beta-lactam antibiotic and emergence of MDR were explored. The visual aspect of the cumulative incidence functions curves suggests increased emergence of resistance associated with de-escalation, although this did not reach statistical significance. Two additional subgroup analyses, one in patients with microbiologically documented infections and one in patients with a treatment duration of more than 5 days, showed that the trend towards more resistance in de-escalation versus continuation disappeared altogether. It is likely that the inclusion of a higher number of short antibiotic exposures in the continuation group introduced bias in the original analyses. As such, we hypothesized that emergence of resistance appears to be directly related to overall antibiotic exposure.

In conclusion, from our analysis, it is clear that in real life (for which observational data are arguably more appropriate than controlled trials), the ecological benefits of de-escalation may be less than what theoretically could be expected. Its effects may be diluted by numerous other factors in the complex setting of intensive care and, moreover, may be offset by unintended consequences of the act of de-escalation, e.g. allowing a longer course of antibiotics. We believe

that the overall larger total antibiotic exposure that we observed in de-escalation episodes may not be due to slower resolution of infection but rather to the physician's perceptions and behavior. In this regard, we also speculate that the higher number of superinfections observed in the de-escalation arm of the randomized, controlled, but unblinded trial by Leone et al. could be due to different judgement of the physician, biased by knowledge of the de-escalation status: i.e., larger uncertainty lowering the barrier for restarting antibiotics. The major problem involved in all antibiotic overuse in healthcare is uncertainty about whether infection is present, which pathogens are involved, and what amount of antibiotic therapy is necessary to give the patient the best chance for a favorable outcome.

We believe that, in order to limit the emergence of resistance, antibiotic use should be restricted on several fronts. Targeting empirical antibiotic therapy to local flora or patient's colonizing status, withholding antibiotics in low-probability infections, shortening overall antibiotic courses, and optimizing pharmacokinetics/pharmacodynamics may have more effect than de-escalation in the narrow definition (see future perspectives). Probably, de-escalation has a place in longer antibiotic courses; yet, exactly how this has to be done (which antibiotic, which dose, which timing and duration) requires further study.

5.B.4 Facilitation of internal stewardship decision-making: identification of potentially unjustified prolonged antibiotic treatment courses

Uncertainty about the presence of an infection in its early phase and the potential involvement of MDR pathogens, has become a recurring theme throughout this thesis. ICU physicians often err on the side of caution in the critically ill patient with suspected infection and as a result the threshold to start antibiotics is rather low. Curtailing overall antibiotic consumption, however, has shown to be primordial in the fight against antibiotic resistance. Over the last few years the focus of the CDC shifted from merely reducing the antibiotic spectrum to a more global antibiotic treatment optimization.[29, 91] Clinicians are encouraged to do a systematic reevaluation of ongoing treatment need, duration, antibiotic spectrum and dosing, 48-72 h following the initiation of an antibiotic treatment ('antibiotic time out').[35, 182]

Over a four-year period, we calculated the percentage of potential overuse of carbapenems, glycopeptides and oxazolidinones. We defined 4 categories of potentially unjustified antibiotic use; (1) prolonged prophylactic therapy, (2) prolonged therapy in low probability infections, (3) prolonged empirical therapy (negative diagnostic cultures) in moderate/high probability infections and (4) prolonged broad-spectrum therapy in microbiologically confirmed infections when de-escalation is possible based on susceptibility results of causative pathogens. Merging of

antimicrobial prescription data, microbiology data and diagnostic information was essential to enable the drill-through-to-detail analysis which was needed to calculate the percentage potentially unjustifiable courses. We found that up to one third of the carbapenem DOT/patient-days was deemed to be redundant, compared to 13% of glycopeptides/oxazolidinones consumption. The toxicity profile of prolonged glycopeptide and oxazolidinone use driving the physician to earlier omission of these agents once culture results become available or remain negative, is only one possible explanation for this observation. It is again important, however, to acknowledge the fact that many factors may influence a physicians' prescribing behavior which may not have been captured in this study. The actual savings in antibiotic use after implementation of this 'antibiotic time out' may eventually turn out to differ from what is anticipated by our calculations. Our results on the other hand guide potential future stewardship actions by giving an estimate of the maximum gain that is potentially achieved by a successful intervention (see future perspectives).

C. THE ROLE OF DATA VISUALIZATION THROUGH COSARA

Aggregation of all infection related data and presentation of this information in a clear overview aims to improve adequate antibiotic decision-making. Previous reports suggest that merely presenting data in an orderly and comprehensive manner at the point of care may improve the performance status of the physician. Evaluation of the clinical impact of data visualization through COSARA, however, is not straightforward. A retrospective analysis comparing antibiotic prescribing practices before and after the implementation of COSARA seems to serve little purpose. First of all, important shifts in antibiotic prescription have taken place over the past few years, driven by multiple factors that may confound our results. In addition, relevant performance metrics e.g. adequacy of empirical antibiotic prescription, antibiotic treatment duration, the emergence of antibiotic resistance or the acquisition of superinfections are very difficult to capture longitudinally without the use of an ESS. The fact that detailed, longitudinal data collection was not in place before the implementation of COSARA hampers meaningful retrospective research. The design of a randomized controlled trial to explore the effect of data visualization raised further concerns; conceptual issues such as the inability to blind physicians and the risk of introducing bias when randomizing physicians or patient (ICU) populations, but also ethical issues such as withholding important information that is uniquely captured through COSARA to a treating physician. Intuitively, the use of clinical dashboards could have improved infection management in our ICU, however until now, clear evidence to confirm this assumption is unfortunately lacking due to the reasons that were outlined above.

"I think the biggest innovations of the 21st century will be at the intersection of biology and technology. A new era is beginning."

Steve Jobs

6 FUTURE PERSPECTIVES

A. FACILITATION OF THE IMPLEMENTATION PROCESS OF STEWARDSHIP INTERVENTIONS

In the introduction of this thesis we outlined the crucial steps in the implementation process of a stewardship intervention (figure 1). Until now, our research has focused on monitoring and the use of large longitudinal datasets to design an ASP. The potential future role of COSARA in the actual implementation of a stewardship action, reporting and education will be touched in the next section.

6.A.1 Active clinical decision support to enhance implementation of a stewardship intervention

Clinical decision support systems (CDSS) are computer systems designed to optimize clinical decision-making at the point of care.[185-187] Correct antibiotic prescribing has proven to be a complex task, especially in the critically ill patient, which requires interpretation and integration of information from different sources and formats. In addition, this process is often hampered by a high degree of uncertainty about the probability of infection, its focus and the causative pathogen. The potential of CDSS in antibiotic stewardship is recognized by infectious diseases societies and further development is encouraged.[188] Over the last few years we have seen a rapid growth in the number of CDSS.[185, 189] These systems range from basic electronic prescribing systems to more advanced decision support tools. The COSARA software lends itself for further development of more complex decision support tasks. In table 17 we list some suggested active interventions in continuation of the ASP interventions that were explored throughout this PhD project (table 16). The interventions are divided in general-theoretical, institution specific and patient specific support. Implementation of each of these interventions must be prepared carefully to increase its chances of success. Additionally, close monitoring after implementation is paramount.

An increased use of COSARA by less experienced end-users and a more active role in antibiotic stewardship, entails some important considerations and responsibilities. We need to acknowledge that until now, COSARA is no commercially available software package. The software will need continuous development, frequent updates and a swift clearance of bugs to guarantee the accuracy of decision support and the trust of the end-user in the added value of

the system. Furthermore, efforts to increase accessibility and user-friendliness of COSARA will have to be made to maximize its potential benefit.

Potential future antibiotic stewardship program interventions
General-theoretical support
Provide easy accessible hyperlinks to educational content: ▪ Spectrum of activity per antibiotic agent ▪ Toxicity profile per antibiotic agent ▪ Intrinsic resistance to antibiotic agents per pathogen ▪ Websites of key organizations in critical care, infection and microbiology ▪ Landmark papers on critical care, infection and microbiology
Institution specific support
Provide easy accessible hyperlinks to institution specific guidelines: ▪ Per infection diagnosis: CAP, HAP, urinary tract infection, meningitis, candidemia, etc. ▪ Per antibiotic agent: o Dosing and therapeutic drug monitoring advice o Ranking with de-escalation advice in case of known susceptibility results
Provide access to executive summary reports on: ▪ Local antibiotic consumption ▪ Local resistance patterns per pathogens and/or linked infection type
Patient specific support
Present treatment algorithm and recent SC to the prescribing physician after completion of the pop-up questionnaire in case of a respiratory infection
Alert as soon as diagnostic culture results and susceptibility patterns become available
Suggest the use of institution specific hyperlinks based on patient's specific diagnosis, administered antibiotic agents and known microbiology results
Alert on day 3 following treatment initiation ('antibiotic time-out')
Suggest thorough re-evaluation of ongoing treatment need on day 3 following treatment initiation in case of: ▪ prophylactic therapy ▪ low probability infection ▪ negative diagnostic cultures

Table 17: Overview of potential future antibiotic stewardship program interventions

CAP: community-acquired pneumonia, HAP: hospital-acquired pneumonia; SC: surveillance culture

6.A.2 Education and reporting

Regular reporting of information on antibiotic prescription and antibiotic resistance to physicians, nurses and other healthcare personnel is recognized as an important component of antibiotic stewardship.[29, 190] Information can be communicated through e.g. educational sessions, interdisciplinary staff meetings and repetitive email correspondence. Regular database queries can be performed and provide the essential information. However, it is important to realize that merely extracting the data from COSARA and presenting this information to healthcare workers will probably not lead to improved clinical care. Additional data processing followed by a multidisciplinary assessment of these results will be needed. It has been demonstrated that education needs to be combined with active stewardship interventions to attain the desired effects.[91]

One-on-one education and individualized feedback may influence antibiotic prescribing even more profoundly.[29, 191, 192] To increase acceptance of these stewardship practices, it is important to create a non-punitive atmosphere and to request the input of the team of prescribing physicians.

B. INVESTIGATION ON THE CAUSAL RELATION BETWEEN INFECTION, ANTIBIOTIC, MICROBIOLOGY AND OUTCOME THROUGH ANALYSIS OF DETAILED DATASETS

Electronic health records (EHR) offer the potential to document the process of care in a longitudinal and detailed way. Through the use of COSARA we were able to compile a comprehensive relational dataset on antibiotics, infection and microbiology. High-quality data are available since January 1st 2013 and collection will continue in the future. The large volume of data offers the opportunity to acquire actionable insight into the complex relationship between antibiotic, infection, microbiology and selected outcome measures. Our data are observational and therefore causal inference is challenging. More advanced statistical models, adjusting for time-varying confounding and complex feedback relationships are required.[193] Close collaboration between statisticians and physicians is essential to produce valid and meaningful results.

Prior cooperation between the Department of Applied mathematics, computer science and statistics and the ICU of the Ghent University Hospital focusing on the causal analysis of longitudinal ICU data, provided controversial, new knowledge on the attributable mortality of VAP.[193, 194] The COSARA dataset permits high level follow-up research in this field.

C. ASSESSMENT OF ANTIBIOTIC PRESCRIBING BEHAVIOR

The concept of antibiotic stewardship was already introduced more than 20 years ago. However, until now, the problem of antibiotic resistance is still far from being contained and many interventions fail to produce sustainable positive effects. In his lecture series, the future of medicine, the US surgeon Dr. Atul Gawande stated that failure in medicine is more likely to be the result of ineptitude (our inability to deliver on existing knowledge) than it is due to ignorance (our lack of knowledge).There is a growing awareness that personal views and social context may have a huge impact on antibiotic prescribing behavior. In order to achieve the desired stewardship results these aspects deserve more attention.[195, 196] COSARA may facilitate a better understanding of the key drivers of prescribing behavior through active querying of prescribers in selected treatment scenarios. As such, we can not only detect certain implementation barriers of stewardship interventions, but we can also try to adjust these interventions to ensure that they are in line with local practices, needs and expectations. A close collaboration between ICU physicians, software engineers and researchers in the behavioral and social sciences will be required.

7 ADDITIONAL SCIENTIFIC ABSTRACTS AND PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

A. ABSTRACTS PRESENTED AT NATIONAL AND INTERNATIONAL CONGRESSES

7.A.1 Can we still use beta-lactam antibiotic monotherapy in complicated intra-abdominal infection?

Isabel De Baere, Liesbet De Bus, Pieter Depuydt, Jan De Waele, Geert Claeys

Poster presented at the 33rd Annual Meeting of the Belgian Society of Intensive Care Medicine. Brussels, June, 2013

Introduction:

Beta-lactam antibiotics with activity against anaerobic bacteria are the cornerstone of empirical and targeted therapy for complicated intra-abdominal infections (cIAI). However, increasing prevalence of extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*, both in community and hospital-acquired infections, and of beta-lactam-resistant enterococci and staphylococci, in hospital-acquired infections, may challenge their appropriateness as empirical therapy.

Objectives:

Comparison of susceptibility of pathogens involved in cIAI to beta-lactam antibiotics in a 2011-2012 dataset with previous data from 2005-2006.

Methods:

We studied antimicrobial susceptibility, as reported from disk diffusion antibiograms, of pathogens isolated from intra-operative, sterile puncture or blood cultures in patients with cIAI admitted to the medical and surgical ICU of Ghent University Hospital in 2011-2012. We compared these recent findings to susceptibility of cIAI pathogens from a 2005-2006 dataset. Antibiotics studied included: amoxicillin-clavulanic acid, piperacillin-tazobactam and

meropenem. We distinguished between community-acquired and hospital-acquired cIAI. We calculated rates of appropriate coverage by amoxicillin-clavulanic acid or piperacillin-tazobactam monotherapy in community-acquired cIAI and of piperacillin-tazobactam or meropenem monotherapy in hospital-acquired cIAI. Appropriate coverage required that all pathogens isolated were susceptible to the administered antibiotic. Enterococci and coagulase-negative staphylococci were considered as pathogens in hospital-acquired cIAI only.

Results:

A total of 132 pathogens were identified in 81 patients admitted in 2011-2012; 45 episodes were polymicrobial. Pathogens involved in community-acquired infection (Gram-negatives only, n=22) were susceptible for amoxicillin-clavulanic acid in 78%, for piperacillin-tazobactam in 93% and for meropenem in 100%. Pathogens involved in hospital-acquired infection (Gram-negatives, n=84, and Gram-positives, n=26) were susceptible for amoxicillin-clavulanic acid in 45%, for piperacillin-tazobactam in 72% and for meropenem in 88%. Amoxicillin-clavulanic acid and piperacillin-tazobactam monotherapy would have adequately covered 86% , respectively 93% of community-acquired infections in 2011-2012. Coverage rates of amoxicillin-clavulanic acid and piperacillin-tazobactam monotherapy for community-acquired infections in the 2005-2006 dataset (n=39) were 81%, respectively 88%. Amoxicillin-clavulanic acid, piperacillin-tazobactam and meropenem would have adequately covered 37%, respectively 73% and 93% of hospital-acquired infections in 2011-2012; coverage rates of amoxicillin-clavulanic acid, piperacillin-tazobactam and meropenem monotherapy for hospital-acquired infection in the 2005-2006 dataset were 43%, respectively 74% and 87%.

Conclusions:

Susceptibility of cIAI pathogens for beta-lactam antibiotics has remained fairly constant over the last five years in our tertiary care hospital. Empirical monotherapy with a beta-lactam antibiotic is still a viable option in cIAI as piperacillin-tazobactam for community-acquired and meropenem for hospital-acquired cIAI. Subsequent de-escalation of piperacillin-tazobactam to amoxicillin-clavulanic acid and of meropenem to piperacillin-tazobactam would be possible in the majority of microbiologically documented cases.

7.A.2 VAP: microbial etiology and outcome

Arif Karakaya, Liesbet De Bus, Bram Gadeyne, Johan Decruyenaere, Pieter Depuydt

Poster presented at the 34th Annual Meeting of the Belgian Society of Intensive Care Medicine. Brussels, June, 2014

Introduction:

A definite diagnosis of ventilator-associated pneumonia (VAP) requires the identification of a microbial pathogen as likely cause of the infection. However, in daily clinical practice at the Intensive Care Unit (ICU), antibiotics are commonly prescribed for a clinical suspicion of VAP in the absence of an identifiable microbial cause.

Objectives:

We compared clinically suspected VAP with documentation of a likely microbial etiology and suspected VAP without microbiological documentation.

Methods:

This study was a retrospective analysis of prospectively collected data between July 1st 2010 and February 28th 2014 in the 36-bed medical and surgical ICU of Ghent University Hospital. We prospectively registered the indication of all antibiotic prescriptions in ICU admitted patients with the aid of the software program COSARA. A clinical suspicion of VAP as reason for the antibiotic therapy required the presence, in a patient ventilated for at least 48 h, of a new or worsening chest infiltrate together with at least two of the following conditions: (1) fever >38.3 °C, (2) leucocytosis >12.000/µl, (3) worsening gas exchange, (4) purulent endotracheal secretions. Microbiological documentation required the presence of a pathogen at least growing 1+ semiquantitatively in a good quality endotracheal aspirate or bronchoalveolar lavage fluid specimen, or isolated from a blood culture at the time of clinical suspicion. Only the first episode of VAP was considered for analysis.

Results:

VAP was clinically suspected in 473 patients, with microbiological confirmation in 250 (53%). A non-fermenting pathogen (NFP) was identified in 84 VAP episodes (18%). Probability of infection was judged as moderate/high (as compared to low) in 92% respectively 69% of VAP

with and without microbiological confirmation (p<0.001). Duration of antibiotic therapy was significantly longer in microbiologically confirmed VAP (7d (5-11) vs. 6d (3-8) (p<0.001)). In patients with and without microbiological confirmation, the number of patients with severe sepsis (15% vs. 10%) or septic shock (16% vs. 11%) was not significantly different (Chi-squared test p=0.12).

ICU mortality was 29% in patients with and 30% in patients without microbiological confirmation (p=0.77) and length-of-stay following VAP diagnosis was 13 (6-22) days and 13 (6-23) days (p=0.8), respectively. Comparing NFP VAP with all other episodes, we found significantly increased mortality (43% vs. 27%, p=0.003) and similar length-of-stay (12 (6-23) days and 13 (6-23) days, p=0.75). After adjustment for severity of infection (sepsis, severe sepsis, septic shock), ICU-mortality was not statistically different between patients with VAP with or without microbiological confirmation, but was significantly higher in NFP VAP patients (OR 1.9 (p=0.014).

Conclusion:

In our center, microbiological confirmation increased the clinician's confidence in the diagnosis of VAP and was associated with a longer duration of antibiotic therapy. A NFP as likely pathogen was associated with increased mortality.

7.A.3 Antibiotic prescription during weekday, night and weekend shifts

Joris Vermassen, Liesbet De Bus, Bram Gadeyne, Johan Decruyenaere, Pieter Depuydt

Poster presented at the 27th Congress of the European Society of Intensive Care Medicine. Barcelona, October, 2014

Introduction:

Antibiotic prescription in the ICU is complex and may be influenced by organizational factors as well as prescriber's subjectivity. During night shifts and weekend shifts, antibiotic prescription may be different from that of weekday shifts due to time pressure, less in-depth knowledge of complex patient files, or lower availability of up-to-date microbiological information. Knowledge of physician's prescription behavior may help to identify potential areas for antibiotic stewardship interventions.

Objectives:

To compare total antibiotic prescription and type of antibiotic prescribed between weekday shifts, night shifts and weekend shifts in a large medical and surgical ICU.

Methods:

From January 1st 2013 to March 31st 2014, all antibiotic prescriptions for newly diagnosed infections at the 36 bed ICU of the Ghent University Hospital were prospectively registered with the aid of the software program COSARA. COSARA was developed to assist the ICU physician in collecting data about antibiotic prescriptions and infection characteristics of ICU patients. Combination therapy was defined as beta-lactam plus a quinolone, glycopeptide or aminoglycoside. Time of prescription was defined as weekday shift (Monday to Friday 8 am to 6 pm), night shift (Monday to Friday 6 pm to 8 am) and weekend shifts (from Friday 6 pm to Monday 8 am or on holidays).

Results:

A total of 1921 infections requiring antibiotic therapy were identified. Total antibiotic prescriptions amounted to 3.12/12 h during weekday shifts, 1.2/12 h during night shifts and 2.4/12 h during weekend shifts. Of these, 25.8 % were associated with severe sepsis or septic shock during weekday shifts, compared to 36.1 % during night shifts and 31.5 % during

weekend shifts (p = 0.003). Carbapenems and piperacillin-tazobactam made up 10.2 %, respectively 31 % of weekday prescriptions, as compared to 14.7 %, respectively 41.7 % of night and 10.1 %, respectively 35.6 % of weekend prescriptions (p = 0.022 for carbapenems, p = 0.002 for piperacillin-tazobactam). The percentages of other antibiotics or of combination therapy did not differ between the three time periods. In a bivariate analysis, carbapenem prescription was associated with severe sepsis (OR 2.791; p < 0,001) and septic shock (OR 2.628; p < 0,001), but not with time of prescription. In contrast, piperacillin-tazobactam prescription was associated with night shift (OR 1.602; p = 0.005), severe sepsis (OR 2.735; p < 0.001) and septic shock (OR 3.443; p < 0.001).

Conclusions:

In our ICU, prescription of carbapenems and piperacillin-tazobactam was more frequent in night shifts as compared to weekday and weekend shifts. Prescription of piperacillin-tazobactam was associated with night shifts when corrected for severity of infection.

7.A.4 Colonization/infection by ESBL producing *Enterobacteriaceae* in ICU

Hannah Schaubroeck, Liesbet De Bus, Bram Gadeyne, Jerina Boelens, Pieter Depuydt

Poster presented at the 37th Annual Meeting of the Belgian Society of Intensive Care Medicine. Brussels, June, 2017

Introduction:

Extended spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL-E) are increasingly cultured from patients admitted to the intensive care unit (ICU) worldwide.[88, 197, 198] Detailed epidemiological data are necessary to assess the impact of ESBL-E in critically ill patients and to evaluate the role of ICU admission in the acquisition of these strains.

Objectives:

We provide a detailed epidemiology of ESBL-E colonization and infection in a mixed adult tertiary ICU population over an 18-month period. We distinguish between import and acquisition in the ICU by taking into account the timing of the first ESBL-E positive culture.

Methods:

We retrospectively analyzed clinical and microbiological data from adult patients admitted to the ICU of Ghent University Hospital between July 2014 and December 2015. Patients who were hospitalized for at least 48 h or who died in the ICU and who had one culture or more yielding ESBL-E were included. All data were prospectively collected using the COSARA software providing linkage between microbiological and clinical data. ESBL-E cultures were considered as early acquired/imported or late acquired when they were isolated within, respectively after two calendar days of ICU admission.

Results:

Out of a total population of 1671 patients, 239 (14.3%) had ESBL-E cultured. In ESBL-E positive patients, ESBL-E was classified as early acquired/imported in the ICU in 69%. The most prevalent ESBL-E species were *Escherichia coli* (80%) and *Klebsiella pneumoniae* (11%). In ESBL-E positive patients, antibiotic therapy for presumed infection was prescribed in 176 (73.6%); in 105 patients, a causative pathogen was identified, which was ESBL-E in 36 (15% of ESBL-E positive patients). The most frequent foci of infection in ESBL-E positive patients were

the respiratory tract (53%), intra-abdominal cavity (18%) and urogenital tract (8%); for infection caused by ESBL-E, these foci accounted for respectively 33%, 31% and 19%. In ESBL-E positive patients, ICU mortality rates in patients with infection caused by ESBL-E and other pathogens were not significantly different (17% and 14%, respectively).

Conclusions:

In our ICU, ESBL-E are mainly acquired early or imported, and their contribution to infection appears to be limited.

7.A.5 A critical analysis of antibiotic therapy in cardiac surgery patients

Maarten Leysen, Liesbet De Bus, Ingrid Herck, Wim Vandenberghe, Harlinde Peperstraete, Bram Gadeyne, Pieter Depuydt

Poster presented at the 37th Annual Meeting of the Belgian Society of Intensive Care Medicine. Brussels, June, 2017

Introduction:

Early postoperative respiratory complications (EPRC) are common in cardiac surgery patients and empirical antibiotic therapy is frequently prescribed for this indication. Antimicrobial stewardship demands restriction of empirical antibiotic therapy in non-infectious EPRC and a good match of empirical choice to local microbiological flora. To assess whether an antimicrobial stewardship intervention might be warranted, we performed a retrospective analysis of antibiotic therapy for presumed EPRC in our cardiac surgery intensive care unit (CSICU). This included an estimation of the probability of infection in EPRC treated with antibiotics and an assessment of pathogen susceptibility to empirical antibiotic therapy.

Methods:

With the help of the software program COSARA, all antibiotic prescriptions in patients admitted to the ten beds CSICU of Ghent University Hospital in 2016 were prospectively recorded, including a preliminary notification of the indication. Presumed infectious EPRC was defined as any antibiotic prescriptions within 72 h of cardiac surgery with a preliminary notification as 'respiratory infection': these were retrospectively classified as postoperative pneumonia of respectively high, moderate and low probability, or as tracheobronchitis; in addition, the absence or presence of diagnostic microbiological cultures was noted and in vitro susceptibility of isolated pathogens to empirical antibiotics was assessed.

Results:

Out of a total of 814 patients admitted to CSICU following cardiac surgery, 118 (14.5%) had presumed infectious EPRC. Of these episodes, 17 (14.4%), 22 (18.6%) and 56 (47.5%) were classified as pneumonia of high, respectively moderate and low probability, and 23 (19.5%) as tracheobronchitis. The most frequently prescribed antibiotics in presumed infectious EPRC were amoxicillin-clavulanic acid (48.3%), piperacillin-tazobactam (33.9%) and cefuroxime (11.0%).

Diagnostic microbiological cultures were available in 64 (54%) patients: in 26 (22%), only commensal flora was found. The most frequent pathogens were *Enterobacteriaceae* and *Pseudomonas spp.*, present in respectively 21 and 9 patients. Empirical antibiotic therapy was appropriate in 49 (77%) patients and had a too broad spectrum in 34 (53%) patients.

Conclusions:

In our CSICU, more than half of EPRC treated with antibiotics could be classified as pneumonia of low probability or as tracheobronchitis, where the benefit of antibiotic therapy is probably limited. On the other hand, empirical antibiotics only had a moderate match with identified microbial pathogens. Both aspects of antibiotic therapy might benefit from an antibiotic stewardship intervention.

B. REDUCING ANTIBIOTIC USE IN THE ICU: A TIME-BASED APPROACH TO RATIONAL ANTIMICROBIAL USE

Pieter Depuydt, Liesbet De Bus and Jan De Waele

Annual Update in Intensive Care and Emergency Medicine 2016 pp 15-23

Introduction:

Antibiotics are life-saving drugs and among the most important therapeutic weapons of the intensive care unit (ICU) physician. In severe bacterial infection, community-acquired, healthcare-associated and hospital-acquired, timely administration of antibiotic therapy active against the causal pathogen is one of the main determinants of a favorable patient outcome. On the other hand, it is an undeniable fact that antibiotics need to be used judiciously, as the induction and rapid spread of resistance threatens to reduce their lifespan. Trying to spare our current antibiotic armamentarium has become urgent, as development of new antibiotics has lagged completely behind the emergence of resistance.[199] As such, the ICU physician faces a daily dilemma: Using antibiotics may improve individual patient outcome (inasmuch as clinical deterioration is due to bacterial infection), but will induce selection pressure and potential harm to future patients or to the same patient in the future, whereas withholding antibiotics will avoid selection pressure but may put the individual patient at increased risk of harm caused by an untreated infection. This dilemma is made worse by the fact that, in critically ill patients, clinical presentation of hospital-acquired infection may be subtle or atypical at the time when the decision of whether or not to start antibiotics has to be made. Moreover, at that time, the causative pathogen is usually not identified but assumed to be potentially resistant to multiple antibiotics. These uncertainties lead ICU physicians to err on the side of caution for the immediate benefit of the individual patient and to accept a certain overuse of broad-spectrum antibiotics. However, as the ecological impact of antibiotic consumption is escalating, efforts have been made to reconcile maximum short-term patient safety (the least number of 'missed' infections or 'missed' pathogens) with a reduction in overall antibiotic use.

As no biomarkers have been identified that can reliably distinguish bacterial infection from other disease at an early stage, the general approach to antibiotic decision-making in the ICU is that of an upfront broad-spectrum regimen followed by de-escalation. Basically, this strategy consists of having a low threshold for starting antibiotics (often several in combination) at

clinical suspicion of infection, covering a wide spectrum of potential pathogens and resistance mechanisms, and subsequently reevaluating when microbiological data become available. This reevaluation considers whether there is a need to continue antibiotic therapy and, if so, whether the initial broad-spectrum antibiotic can be replaced by a narrower-spectrum drug tailored to the identified causal pathogen but causing less selection pressure.[80] The main concept underlying this approach is to strike a balance between immediate patient safety ('more antibiotics') and preserving ecology ('less antibiotics') at each time point, using all the information that progressively becomes available.[200] Although this strategy sounds attractive and logical, there is general agreement that antibiotics are overused in critical care. Indeed, many empirical antibiotic treatments include broad-spectrum agents and de-escalation is performed in only a minority of patients; overall treatment duration is also often longer than deemed necessary. Antibiotic stewardship programs have been introduced to counter these trends and have been advocated by several societies. Practical implementation of these concepts at the bedside is difficult, however. In this chapter, we propose a time-based approach to antibiotic use including the concept of dynamic reevaluation, and we present four key time points at which to (re)consider antibiotic therapy in the ICU (Fig. 17). In this way, antibiotic stewardship philosophy is integrated into the clinical decision-making process.

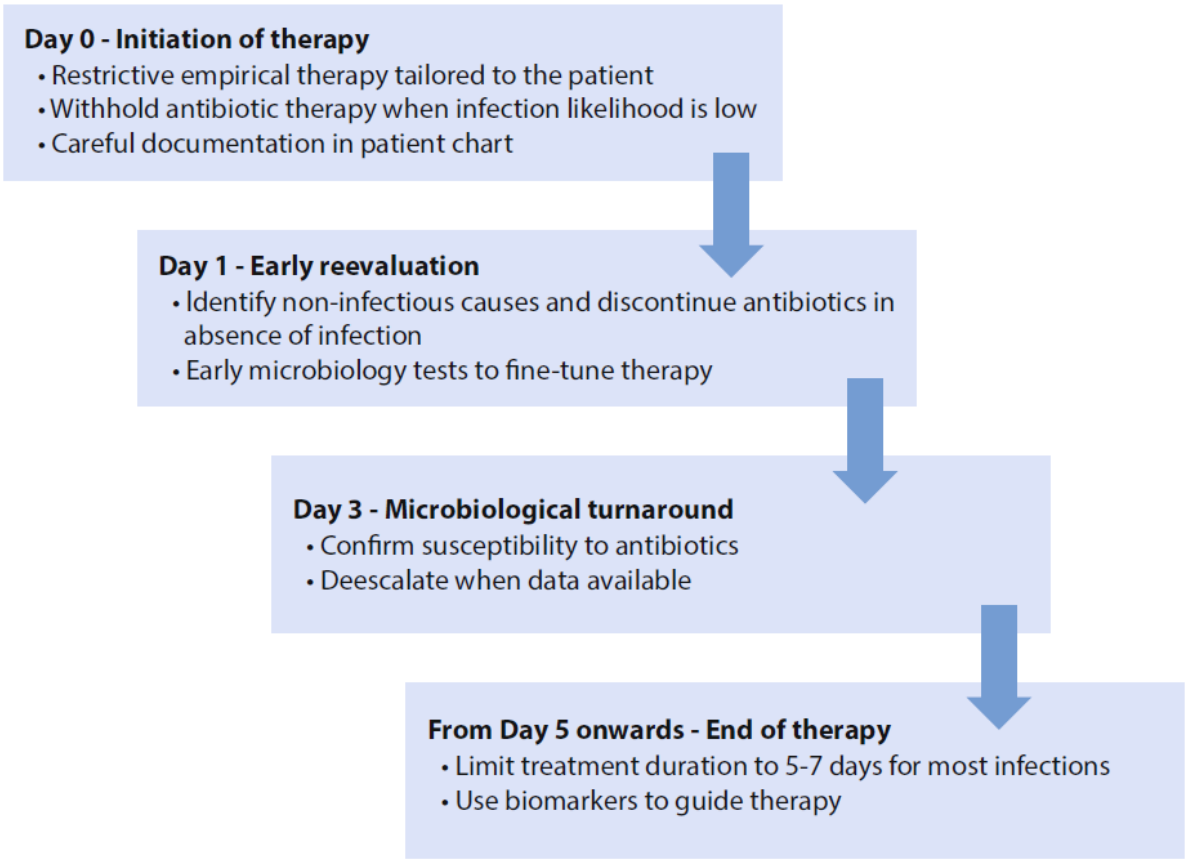

Fig. 17 Opportunities for stewardship during antibiotic decision-making in the ICU

Time point 1: Day 0 – start of empirical antibiotic therapy

Obviously the start of empirical therapy is a first crucial moment of the antibiotic course. The first hurdle to take in an ICU environment is to distinguish sepsis, severe sepsis or septic shock from a systemic inflammatory response syndrome (SIRS) (with or without one or more organ dysfunctions) caused by a non-infectious condition, e.g., in surgical, burn, pancreatitis and trauma patients. If the infectious origin is obvious, there is no doubt that initiation of antibiotics should be an integral component of early treatment. There may be situations, however, in which the infectious origin of the clinical picture is not (yet) clear, and antibiotics may be withheld. The Surviving Sepsis Campaign (SSC) recommendation is largely based on a retrospective cohort study of septic shock patients in which mortality increased per hour delay in administration of adequate antibiotic therapy[201], and should not be lightly extrapolated to patients without septic shock. A recent meta-analysis that included 11,017 patients with severe sepsis or septic shock could not confirm the mortality benefit of starting antibiotics within 1 h of shock recognition and challenges the current SSC recommendation.[202] A multicenter randomized controlled trial (RCT) suggested that the exact timing of antibiotics may be less important when early aggressive resuscitation is achieved.[203] These data support the concept that prompt resuscitation is primordial in any unstable patient, but also that a watchful waiting strategy regarding antibiotic administration beyond the proposed 1 h timeframe may be safe in selected patients when the likelihood of infection is low.

Fears of missing this window of presumed opportunity for life-saving treatment and peer as well as societal pressure to start antibiotics, together with the difficulties in the early recognition of infection, may tempt the physician to take the 'safe and easy' path and start antibiotic therapy from the moment a suspicion of infection is raised. Essentially, the SSC recommendations are for patients who present with severe sepsis or septic shock. On the other hand, patients can suffer from an obvious infection, e.g., peritonitis due to gastrointestinal perforation, without the necessary SIRS criteria, and the need for early antibiotic treatment is not really questioned. However, infection may not always be evident. A before and after observational cohort study – excluding septic shock patients – compared aggressive initiation of antibiotic treatment with a treatment strategy where initiation was withheld until more objective data, particularly microbiological evidence, were obtained.[204] The rate of initial appropriate therapy was higher in the less aggressive arm and mortality was lower, suggesting that a more reserved approach to starting antibiotics in the hemodynamically stable patient with possible infection may be justified. In the Sepsis Occurrence in Acutely ill Patients (SOAP) study, more than half of the patients who received antibiotic treatment during their ICU stay did not have severe sepsis,[205]

implying that a substantial number of patients may in fact be candidates for a more restricted antibiotic initiation as described above.

If the decision to start antibiotics is made, it is important to select an adequate antibiotic regimen covering all expected pathogens. Inevitably in a setting where multidrug-resistance (MDR) is problematic, this will require an antibiotic scheme that includes all potential pathogens even if this exceeds the spectrum of the pathogens that are eventually identified. As an example, international guidelines, such as those published by the Infectious Diseases Society of America (IDSA), propose empirical broad-spectrum and, as a rule, combination therapy for hospital-acquired pneumonia.[80] However, it is pointless to cover microorganisms that are very unlikely given the patient profile and local ecology. Guidelines tailoring empirical therapy to local susceptibility data resulted in increased appropriateness and reduced use of broad-spectrum combination therapy.[136, 142] Furthermore, mapping the patient's colonization status by surveillance cultures may reduce the use of broad-spectrum regimens.[137, 162] Therefore, in the current situation of a worldwide, but very inhomogeneous spread of MDR, customizing these (inter)national guidelines to local institutional and patient ecology may offer an opportunity to reduce antibiotic use from the very start.

This decision-making process is complex and, as such, should be carefully recorded in the patient's file. To facilitate decision-making later in the course of therapy, it is essential to obtain all relevant microbiological cultures at this stage and preferably before the start of antibiotics to document the infection and identify the causative pathogen.

Time point 2: Day 1 – early reevaluation

After 24 h of antibiotic therapy, we advocate a systematic clinical reevaluation of the patient to confirm (or not) the presence of infection. As signs and symptoms suggesting infection in critically ill patients may be non-specific, alternative diagnoses should always be considered from the very start, whether or not clinical deterioration calls for immediate start of antibiotics. A 24 h window may be a good moment to reevaluate the patient, as the evolution of the clinical picture often allows better differentiation between infectious and non-infectious causes of deterioration or SIRS. This offers an opportunity to discontinue antibiotics that were –in retrospect – initiated inappropriately and will depend on the level of certainty that infection was present when antibiotics were initiated. In patients who are not improving, a careful search for an alternative diagnosis is important and is to be preferred to blind escalation of antibiotic therapy when clinical signs and symptoms do not respond favorably early after start of antibiotics. If there is another clear cause of the current condition or deterioration of the patient,

then antibiotics should not be continued. A typical example of this would be a patient with pancreatitis, who may present with acute abdominal pain and who may receive early empirical antibiotic therapy for suspected infection but who is found to have pancreatitis only, without signs of infection and without the need for antibiotic therapy.

At this point also, the results of microbiological studies may become available, which can help to guide therapy. These include simple techniques such as direct examination with Gram-stain and direct antibiogram but also more sophisticated techniques, including matrix assisted laser desorption ionization time-offlight (MALDI-TOF) and polymerase chain reaction (PCR) based techniques. The cost-effectiveness of these techniques at this point is unclear. Using this approach creates a second opportunity to treat less obvious pathogens and may also allow the identification of MDR pathogens, such as *Acinetobacter* and *Stenotrophomonas* spp. or fungi, which may not be covered by the spectrum of the antibiotic administered.

Direct Examination and Gram-stain of Samples

Although the information that can be obtained from a Gram-stain may appear limited, it may assist the clinician in directing empirical antibiotic therapy as well as in assessing the need for other interventions. This technique can be applied to several types of samples, including respiratory and abdominal samples. Direct examination may suggest the presence of microorganisms that are not covered by the initial treatment strategy and this is, therefore, particularly helpful in a restricted empirical antibiotic strategy.

Direct Susceptibility Testing

Rather than the susceptibility of one pathogen, direct susceptibility testing reflects the susceptibility of the microbial community in a sample. Although there are some limitations to this technique, direct susceptibility testing using direct inoculation of the clinical sample may provide early information on susceptibility and reduce turnaround time by 24 h.[206]

MALDI-TOF

This recently introduced proteomics-based technique allows rapid determination of pathogens after culture.[207] Again this may not provide any details on susceptibility but may point the clinician to the presence of unexpected pathogens.

PCR-based Techniques

Several commercial tests have been developed in recent years and most allow identification of pathogens with 8 h of sampling. A recent systematic review and meta-analysis of the available studies on one of the most studied tests found the test to be of limited value to exclude infection

in the critically ill;[208] nevertheless, this test may allow identification of pathogens that have limited susceptibility to the empirical regimen. Susceptibility information is not available from these PCR-based techniques (except for the presence of the MecA gene for methicillin-resistant *Staphylococcus aureus* (MRSA)). It should be noted that most of the studies in this field have been conducted in patients with bloodstream infection only and the value in other infections remains to be determined.

Time point 3: Day 3 – microbiological turnaround

At 72 h the picture is usually complete, with all relevant culture results available in most situations. This is the pivotal moment for reassessing likelihood of infection as well as streamlining antibiotic therapy.

Similar to the 24 h time point, the presence of infection may be reconfirmed but again alternative diagnoses may be considered. Clinicians may decide, based on the available information, that infection may not have been present, and stopping antibiotics is definitely an option in selected patients. Although there is often reluctance to stop antibiotic therapy once started, an RCT from 2000 already showed this to be safe.[209]

This is usually also the time point when the susceptibility pattern of the pathogen is available and definite antibiotic therapy can be decided. Apart from changing the antibiotic in case of resistance to the pathogen, this offers an opportunity to stop unnecessary antibiotics – antibiotics that do not cover the pathogen involved but were part of multidrug empirical antibiotic therapy, e.g., vancomycin as part of an empirical broad-spectrum regimen for hospital-acquired pneumonia. Similarly, in patients who have been treated with combination therapy, e.g., a beta-lactam antibiotic plus an aminoglycoside, it may be the appropriate time to stop the more toxic antibiotic.

De-escalation of antibiotic therapy, or changing the antibiotic to another agent with a smaller spectrum, has been advocated as an essential element of antibiotic stewardship programs.[90] As such, it will reduce the use of broad-spectrum agents and presumably reduce selection pressure. In clinical practice, however, de-escalation is only used in 13 to 43% of patients in most studies.[94] De-escalation has been associated with decreased mortality in critically ill patients but a causal effect is unlikely.[157]

Time point 4: from day 5 onwards – end of the antibiotic course

If antibiotics are continued beyond 72 h, it is assumed that infection is present and that a complete antibiotic course is necessary. However, the optimal duration of such a course is at present not known and is probably dependent on pathogen load and susceptibility, focus and tissue extension of the infection, host defense mechanisms and whether or not some form of source control can be achieved. Extending antibiotic therapy must balance the possible benefit of achieving better microbial control against the harm of promoting resistance by prolonging selection pressure. As most of the current evidence relates patient outcome to treatment determinants that appear at the 'head' of antibiotic therapy (timing/initiation of therapy, appropriate empirical choice), the 'tail' of antibiotic therapy may offer the best opportunities to reduce overall antibiotic exposure without compromising patient outcome. As such, in the more recently published literature, there is a clear tendency to decrease duration of antibiotic courses. This trend is best documented for pneumonia. A landmark RCT in patients with ventilator-associated pneumonia (VAP) found that an 8-day antibiotic course did not result in worse patient outcome as compared to a 15-day course; the rate of infection recurrence was higher for *Pseudomonas* infections, but this was not associated with increased mortality or length of stay.[210] This result provides firm ground for the recommendation to set a stop at day 8 of antibiotic therapy for pneumonia, counting from the first day of appropriate therapy. Although data from RCTs are lacking, the SSC recommend a similar 7 to 10 day course of antibiotic therapy as a standard for all nosocomial infections, to be modified in the light of clinical response and microbiological data.[90, 211] However, these guidelines are only slowly changing daily practice, as the mean duration of a 'usual care' antibiotic course in the ICU (gleaned from observational studies and control arms of interventional studies) still exceeds these times.[212, 213]. Recommendations for shorter antibiotic treatment courses may be most effective when translated into a default stop date for antibiotic therapy, with continuation of antibiotics beyond this date only for selected indications or clinical situations. Apart from some clearly defined clinical infections for which prolonged antibiotic treatment is standard of care (such as endocarditis or prosthetic joint infection), longer antibiotic courses may be required in situations with extensive and persistent tissue inflammation together with lack of microbial eradication, such as necrotizing pulmonary infections, persistent gastrointestinal leaks or inaccessible infection foci. For this latter category, however, it should be recognized that there is no evidence that prolonged antibiotic courses improve outcome beyond standard courses, and continued efforts to achieve source control (preferably as early as possible in the course of the treatment) may be more effective.[214] As mentioned before, a decision to stop or continue antibiotics should be formally noted in the patient's clinical files to allow subsequent reevaluation.

Several RCTs have compared antibiotic courses prescribed as usual care with an approach focusing on antibiotic stopping, using algorithms taking into account the evolution of biomarkers or clinical parameters. Serial measurements of procalcitonin (PCT) with an algorithm recommending that antibiotics be stopped when PCT concentrations decrease below a certain threshold or percentage from its peak value, can be used to reduce the duration of the antibiotic course to a median of 6 days.[215] When PCT is not available, serial clinical evaluations may achieve the same goal, at least for respiratory infections.[216] Most importantly, during daily clinical rounds in the ICU, all ongoing antibiotic prescriptions should receive a critical evaluation by the attending physician.

Conclusion:

Decision-making about initiation, changing and stopping antibiotic therapy in the ICU is a complex activity due to its dual goal – eradicating pathogenic bacteria causing serious infection versus minimizing promotion of antimicrobial resistance caused by selection pressure – and due to the uncertainties surrounding clinical diagnosis of infection and its causal pathogen(s). There are, however, several opportunities to reduce unnecessary antibiotic exposure while preserving patient outcome. The principle of de-escalation is currently the main answer to this diagnostic and therapeutic problem. However, it is important to tailor this principle to the individual clinical case and avoid unnecessary antibiotics as much as possible. This goal is best achieved by a dynamic approach with critical reassessments of the need for and choice of antibiotics at preset time points while actively pursuing diagnostics and integrating all the available information. This proposed time-based approach is a convenient way to translate different aspects of antimicrobial stewardship into clinical practice at the bedside.

C. CONTROVERSIES IN VENTILATOR-ASSOCIATED PNEUMONIA DIAGNOSIS

Pieter Depuydt and Liesbet De Bus

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Ventilator-associated pneumonia (VAP) is a major complication of mechanical ventilation and represents the most common reason for antibiotic prescription in ventilated patients. Incidence ranges from 1.2 to 8.5 cases per 1000 ventilator days or 9 to 27% cases per mechanically ventilated patient; attributable mortality rates vary between 0% and 70%.[217, 218] The large variability of these figures stems from the fact that both development and outcome of VAP result from a complex interplay between pathogens and host under the influence of many factors: comorbidities, severity and cause of the underlying critical illness, its treatment and its evolution over time. Additionally, uncertainty surrounds diagnosis of VAP and many different diagnostic strategies and criteria prevail. Clinical signs and symptoms, biochemical markers of inflammation and radiological signs of alveolar consolidation, which are highly accurate for a diagnosis of pneumonia in a walking patient in the community are much less so in the critically ill patient under mechanical ventilation. Clinical and biochemical alterations may be absent, or may have an alternative cause that can be infectious or non-infectious. An infiltrate on chest X-ray is required for diagnosis, as it has high sensitivity, but is remarkably non-specific. Inter-observer variability of chest X-ray interpretation is large, especially when it comes to deciding whether or not an infiltrate is 'new', 'evolving' and represents alveolar consolidation. Increasing the number of diagnostic criteria required for diagnosis gains specificity at the cost of reduced sensitivity. The Clinical Pulmonary Infection Score (CPIS) is a quantification of these criteria in a summary score: a higher CPIS score increases the likelihood that VAP is present, but no single cut-off combining a high sensitivity with a high or acceptable specificity can be identified.[219] Despite decades of study and an impressive amount of published data, the question of how VAP can be accurately diagnosed is not definitively settled. In this contribution, four controversies regarding VAP diagnosis are briefly discussed.

Invasively obtained microbiology allows accurate diagnosis of VAP

Adding microbiological data increases specificity of VAP diagnosis.[217] However, the presence of a potential pathogen in a respiratory sample of a mechanically ventilated patient is in itself no proof for VAP, as it may represent colonisation of lower respiratory airways or contamination by flora residing in the upper respiratory tract or in the biofilm on the endotracheal tube. Invasive diagnostics in VAP refer to the use of fiberoptic or blind bronchoalveolar lavage (BAL) or protected specimen brush in order to sample more selectively the distal airways and alveoli. Using these samples for direct examination for the presence of intracellular pathogens in alveolar macrophages or polymorphonuclears and for quantitative culturing further helps to distinguish between colonisation and infection.[217, 220, 221] As such, quantitative cultures of invasively obtained samples may improve the specificity of VAP diagnosis more than qualitative culture of routinely obtained endotracheal aspirates. However, the selection of a threshold for quantitative cultures to discriminate between infection and colonisation again must strike a balance between specificity and sensitivity. Thresholds for diagnosing VAP may differ between populations. For example, some authors have argued in favor of using a higher threshold ($>10^5$ colony-forming units (CFU)/ml) in BAL samples of trauma patients than the one usually applied in medical patients ($>10^4$ CFU/ml), to reduce the number of false positives.[222] On the other hand, in patients who received antibiotics prior to their BAL, the quantitative threshold for VAP diagnosis should probably be lowered to limit the number of false negatives. However, in the absence of a true gold standard for the diagnosis of VAP, test characteristics of invasive microbiological techniques are not well established. Quantitative cultures themselves are often used as a form of gold standard to which other diagnostic tests are compared, which may lead to a form of circular reasoning.[221] Regardless of the higher specificity of invasive microbiology, clinical characteristics must always be taken into account for a diagnosis of VAP, as many patients with prolonged mechanical ventilation have a high burden of bacteria in the lower airways without signs of infection.[223]

Invasively obtained microbiology improves outcome in VAP

Proponents of invasive diagnostic strategies in VAP have argued that these techniques improve patient outcome. The outcome benefit is attributed to the higher diagnostic specificity, which helps the attending physician to avoid unnecessary antibiotics and/or direct a search for alternative diagnosis if VAP is refuted.[224] In a recent study, diagnostic workup of clinically suspected VAP with invasively obtained quantitative cultures below threshold led to an alternative diagnosis in 60% of cases.[225] Proponents of noninvasive diagnostics state that the

main treatment factor influencing outcome is timely and appropriate empirical antibiotic therapy directed at all likely involved pathogens; microbiological data serve only to guide subsequent de-escalation of antibiotics. For this purpose, routine endotracheal samples and semiquantitative cultures may suffice.[226] In this view, invasive sampling adds little benefit for the patient and has the disadvantage of increased costs and potentially delayed effective therapy. A meta-analysis comparing invasive and noninvasive strategies for VAP diagnosis found no difference in outcome, but this has not settled the controversy.[227] Recently, the need for antibiotic stewardship measures in VAP management has revived the discussion. Identification of the causal pathogen of VAP has been identified as the main factor promoting de-escalation of empirical antibiotics. As invasively obtained microbiological cultures are more likely to represent the true causal pathogens of VAP compared to cultures from noninvasive samples, the physician may be given greater confidence to de-escalate. Giantsou et al. indeed found higher de-escalation rates in patients subjected to BAL instead of endotracheal aspirates.[158] In addition, the higher specificity of quantitative cultures in suspected VAP, translating into fewer false positives, would also lead to fewer unnecessary antibiotic treatments.[228] However, in the Canadian Critical Care Trials Group trial, which randomized between an invasive and a noninvasive strategy for VAP diagnosis, no differences in the rate of de-escalation or antibiotic stop were found between both arms, nor was patient outcome different.[226] In addition, increased focus on antibiotic stopping whenever possible, using repeated clinical evaluations, or a protocol guided by sequential procalcitonin measurements may achieve a major effect without the use of invasive microbiology.[209, 216, 229]

Ventilator-associated tracheobronchitis (VAT) is a separate condition of VAP

The observation that patients may have all clinical signs and symptoms of VAP and respond to the microbiological criteria of VAP in the absence of unambiguous infiltrates on chest X-ray has led to the concept of ventilator-associated tracheobronchitis (VAT). VAT represents a more limited infection of the lower respiratory tract in ventilated patients. The association between VAT and mortality is less obvious than in VAP, yet VAT appears to be associated with a longer duration of mechanical ventilation.[230] It is not clear whether VAT represents a precursor or early stage of VAP, i.e. whether untreated it proceeds to VAP, or whether it is a milder stage of infection, sitting in the continuum between lower respiratory tract colonisation and clear-cut VAP.[231] Moreover, as the absence of a new or worsening infiltrate on chest X-ray makes the only distinction between VAT and VAP, inter-observer variability may lead to false classification of VAP as VAT. VAT may progress to VAP in a third of cases;[232] antibiotic treatment of VAT thus may prevent evolution to VAP in some patients but may not influence outcome in others. Given

the necessity to restrict antibiotics as part of antibiotic stewardship, treatment of VAT is not straightforward. Antibiotic therapy in VAT, e.g. as delivered by inhalation or systemically as a short course, may prevent full VAP and thus have an overall antibiotic-sparing effect.[233, 234] On the other hand, a strategy in which VAT routinely is considered as an indication for antibiotic therapy will increase the number of antibiotic prescriptions in patients who will not directly benefit from it, but still are exposed to the harmful effects of antibiotics, especially increased selection pressure.

Ventilator-associated events (VAE) are a better concept for monitoring of quality of intensive care

The lack of accuracy of diagnostic criteria of VAP, and especially the inter-observer variability of chest X-ray interpretation hampers the use of VAP as a quality indicator for benchmarking intensive care unit (ICUs). Ego et al. found that VAP incidence in their ICU population varied tremendously according to the different sets of diagnostic criteria used.[235] Reports about achieving zero VAP rates may thus reflect the use of overly specific (and too little sensitive) diagnostic criteria rather than true absence of VAP. This has led to a radical change in the Centers for Disease Control and Prevention (CDC) approach to surveillance of complications of mechanical ventilation, dismissing subjective criteria (such as chest X-ray interpretation) and broadening the concept of VAP to that of VAE. VAE refers to a respiratory deterioration of a mechanically ventilated patient after initial improvement and stabilization, and is diagnosed on the basis of more objective criteria such as ventilator settings and oxygenation indices: this deterioration may or may not be due to infection. A new definition of VAP is tied within this framework and is defined as VAE together with signs of inflammation or newly started antibiotics, purulent secretions and presence of pathogens in respiratory cultures: the label 'possible VAP' and 'probable VAP' is applied if only one, and two respectively, of the last two criteria are met. Studies have shown that VAE poorly correlate with 'traditionally diagnosed' VAP: less severe VAP is missed by VAE and a large number of VAE are not due to VAP.[236] On the other hand, Bouadma et al. found a good correlation between VAE and antibiotic consumption in their multicentre OUTCOMEREA database, suggesting that VAE could represent a proxy for true VAP.[66] Whether or not VAE is preventable is a matter of discussion; this is however a cardinal prerequisite or its use as a quality indicator.[60]

D. HOW TO TREAT INFECTIONS IN A SURGICAL INTENSIVE CARE UNIT

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ABSTRACT

The management of infections in surgical intensive care unit patients poses specific challenges. Although the overall approach to the patient is no different from other patients, diagnosis is often problematic. As in other infections, multidrug-resistance is increasingly described, and changes in pharmacokinetics may require different dosing strategies. Also the need for source control adds a level of complexity to the management of the patient. Whereas source control was a purely surgical issue before, percutaneous drainage has emerged as an important alternative. Appropriate timing of source control often remains difficult to determine, but in most severe infections source control should not be delayed. But also the need for a multidisciplinary approach can make the decision making difficult. New concepts such as dedicated source control teams may further assist in selecting the most appropriate treatment strategy and further improve outcome of surgical severe sepsis patients.

REVIEW

Introduction

Severe infections in surgical patients may be the reason for admission in some, but may also develop during intensive care unit (ICU) stay in others. These infections are an important burden in modern critical care, in terms of morbidity, mortality and resource use. In a recent study from China, mortality was high in surgical ICU (SICU) patients developing severe sepsis (48.7%)[237] and nursing workload high.

Abdominal infections more in particular, are associated with a long ICU stay, more shock and acute kidney injury and a higher mortality compared to other infections [205, 238] and therefore deserve proper attention.

Although there are no standardized definitions of what constitutes SICU patients, patients admitted after recent surgery (within the preceding 2-4 weeks, including emergency surgery (a

non-scheduled operation within 24 hours of the onset of symptoms or injury) are considered surgical [2, 205] and the focus of the current review.

The overall approach to infections in surgical patients is comparable to other patient categories, with rapid administration of appropriate antibiotics as one of the most important elements. The role of source control however should not be underestimated and is to be considered more often. To this extent, communication and interaction with other specialties such as surgery and interventional radiology is pivotal and preferably these patients should be managed in a multidisciplinary way. Diagnosis, both of primary infections or infections where the initial therapy has failed are particularly challenging but also the application of other, newer concepts such as antimicrobial de-escalation may be different.

Rather than listing antibiotic therapy schemes for commonly encountered infections, we will review specific aspects of the treatment of infections in SICU patients.

Epidemiology of infections in surgical ICU patients

SICU patients apparently are at the highest risk to be diagnosed with an infection, presumably because the infection itself was the cause for admission to the ICU more often; as an example, in the Sepsis Occurrence in Acutely ill Patients (SOAP) study, 89% of the abdominal infections were non-ICU acquired [205], the highest percentage of frequently encountered infections studied. In the European Prevalence of Infections in Intensive Care (EPIC)-II study, about two thirds of the infected patients were considered surgical patients (emergency surgery mostly, but also trauma and elective surgery).[2] Obviously not all of these patients had typical surgical sources of infection. In a large study from China, abdominal infections accounted for 72 percent of the infections in SICU patients diagnosed with severe sepsis, with acute pancreatitis and gastrointestinal perforation as the leading sources of infection.[237] Notably more than half of the cases had infections in multiple locations.

As the sources of infections are different compared to general ICU patients, these SICU infections also have a distinct microbiology pattern. Cheng et al. found that 43.7% of infections were polymicrobial, with a comparable contribution of Gram-positive and Gram-negative bacteria.[237] Fungi were also present in a considerable number of infections in this multicenter study (28.3%). In the SOAP study, Gram-positive bacteria (mainly *Streptococcus* D) and *Escherichia coli* were more frequently isolated in surgical patients.[205]

Diagnosing infections in surgical ICU patients

Typically, SICU patients with infectious complications are either admitted with an infection (mostly postoperative) or they develop it during their admission for another primary diagnosis. Both categories pose specific problems in terms of timely diagnosis to allow early therapy.

Diagnostics of infections in SICU patients admitted for non-infectious reasons can be puzzling as the tools we tend to rely on are unreliable in many situations. SIRS criteria are non-specific and frequently a reflection of postoperative inflammation, trauma, burns or any other inflammatory process. Similarly, conventional biomarkers of inflammation are often useless to diagnose infections immediately after another event. Also signs of impending organ dysfunction in a setting of severe sepsis, such as hypotension or oliguria, may be the result of other postoperative complications such as bleeding, fluid losses or under-resuscitation.

In patients admitted after surgical (or interventional) treatment, the diagnosis of recurrent infection due to failed source control is a problem that poses particular challenges. In a prospective multicenter study, Van Ruler et al. found that – contrary to what one may think – the extent of peritonitis, the source of the infection, the type of contamination or operative variables such as the presence of an anastomosis, were not associated with recurrent infection. Adding postoperative symptoms such as fever and parameters of organ dysfunction to the multivariate model, could identify patients requiring additional source control measures.[239] Most commonly used scoring systems perform poorly in this setting, only acute organ dysfunction scores such as the SOFA score were somewhat useful,[240] although the AUROC was only 0.61 for the best discriminative score. Biomarkers may be superior in identifying patients without surgical source control; in a small study Novotny et al. found that a ratio of PCT on day 2 to PCT on day 1 of 1.03 or higher could discriminate failed from effective source control.[241]

Clinical suspicion is probably best to track failed source control early; when available, PCT can be used for confirmation, but further work up remains necessary. Bedside ultrasound and abdominal CT scan represent the best tools; ultrasound has the advantage that it is readily available in most units and does not require transportation to the CT lounge and contrast administration. Both imaging techniques can be complemented by fine needle aspiration of suspected collections, or percutaneous drainage (PCD) in case of collections amenable to catheter treatment. In most situations, PCD is preferable over open surgery to confirm the diagnosis.

Antibiotic therapy

Similar to the general ICU population, the empirical antibiotic scheme should cover the probable pathogen(s). This knowledge needs to be supplemented with local ecology data to determine the most appropriate empirical antimicrobial regimen. In abdominal infections inadequate antimicrobial therapy is associated with an increase in mortality rates in several studies.[242-244] As in other infections involvement of multidrug-resistant (MDR) pathogens is a major concern. Seguin et al. found this risk to be particularly elevated in patients who were hospitalized for 5 days or longer and after previous exposure to antibiotics; when both criteria were present MDR was present in 38% of the infections compared to 2% when both were absent.[245] Swenson et al. reported an association between health-care exposure; e.g. current ICU admission, hospitalization for more than one week, but also including hospitalization within one month prior to the infection, residence in a nursing home or rehabilitation facility, and the occurrence of MDR pathogens.[246]

When selecting empirical and directed antimicrobial therapy in the setting of surgical infections, we have to take some limitations of the microbiology diagnostic techniques into account. Abdominal infections are typically polymicrobial with both Gram-positive and Gram-negative, aerobe and anaerobe bacteria contributing in most patients. Depending on the techniques used, up to 10-15 microorganisms can be found in cultures from intra-abdominal infections, but pathogenicity may be difficult to assess. Anaerobe microbes are difficult to culture and even if these are not reported by the microbiology lab, these should be covered by the antibiotic therapy.[131] This is equally relevant in necrotizing skin and soft tissue infections where an important part of infections are polymicrobial.[247]

De-escalation can be a challenging issue in SICU patients. As discussed above, infections are often present in multiple sites, and are often polymicrobial, limiting the possibilities of de-escalation in these patients. This was found in an earlier study from our center where abdominal infection and the lack of conclusive microbiology were important obstacles to de-escalation.[150]

In recent years the changes in the pharmacokinetics in critically ill patients has received increased interest.[248] Although these changes are not limited to surgical patients, again specific issues should be considered in SICU infected patients as it may impact outcome.[249] One of the main determinants of decreased exposure to antimicrobial therapy is increased elimination of the antibiotic (mostly beta-lactam antibiotics) through a phenomenon of augmented renal clearance. Augmented renal clearance is a frequent finding in critically ill patients and certain categories of SICU patients such as trauma and burn patients.[250] In specific patient populations e.g. following abdominal surgery, increased fluid losses though abdominal drains may further

decrease antibiotic concentrations.[251] Different dosing strategies such as extended or continuous infusion may be required to improve antibiotic exposure in patients treated with beta-lactam antibiotics.[248, 252]

Source control

Source control frequently is an essential element of the therapy of severe infections in surgical patients. It refers to controlling the source of the infection and includes drainage of pus and inflammatory material as well as debridement of necrotic (infected) tissue. Restoration of anatomy and function is equally important and often these components can be combined in one operation. Source control should be considered in all patients with severe infections in the SICU. Although the relevance of source control is not limited to SICU patients, the probability that this patient group requires source control is higher due to the high prevalence of abdominal and other surgical infections.[237]

As a rule of thumb, source control measures should not be delayed except in situations where demarcation of nonviable tissue and infection is preferable, such as infected pancreatic necrosis, or in situations where source control is difficult to obtain, e.g. an infected driveline of a left ventricular assist device (LVAD). The Surviving Sepsis Campaign (SSC) guidelines suggest that patients should be treated within 12 h,[90] but there is no rationale to defer the intervention unless patient's physiology is severely impaired and associated with an unacceptable risk of complications during the source control procedure such as coagulopathy or life-threatening metabolic disorders. Comparable to the effect of postponing initiation of antibiotic therapy in case of hypotension, there seems to be a linear increase in mortality when source control is delayed.[253] Timing of source control is often debated and should be guided by the severity of illness (or rapidity of deterioration), the (presumed) source of infection and the physiologic status of the patient (Table 18). Source control interventions may include surgery but also other measures can be – initially – adequate such as PCD or removal of infected tissues or devices.

Table 18 Urgency of source control intervention (after [254])		
Level of urgency	**Timing of intervention**	**Context**
1	<1-2 h after diagnosis	Rapidly progressive disease e.g. necrotizing fasciitis, intra-abdominal infection with abdominal compartment syndrome
2	As soon as patient physiology allows	Limited deferral is acceptable provided antibiotics are administered and patient is not deteriorating e.g. peritonitis
3	As soon as infectious process has demarcated	Adequate source control is facilitated and probability of collateral damage lower e.g. infected pancreatic necrosis in a stable patient

Therefore it is crucial that institutions that care for these severely ill patients should have 24/7 access to all diagnostic imaging techniques as well as interventional radiology and surgery. Although practical issues such as operation theatre availability and the lack of expertise are often mentioned as reasons why source control is delayed, there is no scientific evidence that delaying source control is safe, even under broad-spectrum antibiotic coverage. Moreover, in the era of increasing MRD infections, administering antibiotics to patients in whom the source is not controlled could lead to the emergence of antibiotic resistance, or selection of less susceptible microorganisms.

Although once considered a surgical issue, source control measures are no longer limited to the operating theatre. Ultrasound or CT-guided PCD is now an important tool in the early management of severe infections in critically ill patients. Its exact role however remains to be determined, and for many infections a surgical procedure still should be considered the standard of care. PCD however can be a helpful tool during initial resuscitation and correction of metabolic disorders, but also for more difficult to surgically treat infections such as infected pancreatic necrosis, where PCD has emerged as the preferred initial therapy and can effectively avoid surgery in a considerable number of patients.[255]

To fully understand the impact of the role of source control in critical care, more attention to this aspect is urgently needed in studies reporting on the outcome of infected patients. Quantifying the residual infection after source control could be helpful to evaluate the role of certain interventions and to guide antibiotic therapy. To this extent we suggest using a classification system (Table 19) that allows to better describe the net effect of source control measures. In analogy with oncological surgery where the R classification reflects the completeness of the surgical procedure, the proposed categorization of residual infection reflects the effect of the source control intervention, supports planning of future treatment and correlates with

prognosis. The presence of residual infection refers to the presence of pus, infected tissue after the source control procedure e.g. incomplete drained abscess after PCD or residual necrotic material that cannot be debrided. Ongoing contamination refers to a source that maintains the infection, e.g. a gastrointestinal tract perforation that cannot be transformed into a fistula and continues to soil the abdominal cavity.

Table 19 Source control categorization

Source control-status	Description
S0	No residual infection
S1	Residual macroscopic infection, no ongoing contamination
S2	Residual macroscopic infection and ongoing contamination

Source control treatment options have been poorly investigated before they entered clinical practice. PCD for example has been studied to some extent in severe acute pancreatitis as part of a step-up minimally invasive approach as opposed to open surgery but for other indications no randomized studies have been performed. Novel interventions should be subjected to rigorous clinical trials but also treatment strategies that have been taken for granted require re-evaluation. Van Ruler et al. compared the often applied planned relaparotomy approach to a more restrictive on-demand relaparotomy strategy and found the latter to be superior in terms of morbidity and cost.[256]

As source control in critically ill is becoming increasingly complex, we advocate the development of multidisciplinary source control teams where intensivists, infectious disease specialists, surgeons and interventional radiologists discuss the need for, the timing of and the preferred methodology used for source control procedures. Continued multidisciplinary evaluation is crucial.

CONCLUSIONS

In conclusion, the management of infections in surgical patients poses specific challenges. Diagnosis is often problematic and the need for source control adds a level of complexity to the management of the patient. Also the need for a multidisciplinary approach can make the decision making difficult. The lack of data have so far led to vague recommendations regarding source control, and clinical studies need to report source control methodology and efficacy. New concepts such as dedicated source control teams may further assist in selecting the most appropriate treatment strategy and further improve outcome of severe sepsis patients in the SICU.

8 LIST OF ABBREVIATIONS

A

ACD:	administrative coding data
APACHE:	acute physiology and chronic health evaluation score
ARDS:	acute respiratory distress syndrome
ASP:	antibiotic / antimicrobial stewardship program
ATS:	American Thoracic Society

B

BAL:	bronchoalveolar lavage
BSI:	bloodstream infection

C

CAS:	computer-assisted surveillance
CDC:	Centers for Disease Control and Prevention
CDSS:	computerized clinical decision support system
CFU:	colony-forming unit
cIAI:	complicated intra-abdominal infections
CIE:	cumulative incidence estimate
CIF:	cumulative incidence functions
CLABSI:	central line-associated bloodstream infection
COSARA:	Computer-based Surveillance and Alerting of infections, Antimicrobial Resistance and Antibiotic consumption in the ICU
CPIS:	clinical pulmonary infection score
CPOE:	computerized physician order entry
CRP:	C-reactive protein
CSICU:	cardiac surgery intensive care unit

D

DOT:	days of therapy

E

EHR:	electronic health record
EPRC:	early postoperative respiratory complications
ESBL:	extended spectrum beta-lactamase

ESBL-E: extended spectrum beta-lactamase producing *Enterobacteriaceae*

ESICM: European Society of Intensive Care Medicine

ESS: electronic surveillance system

ETA: blind end tracheal aspirate; endotracheal aspirate

F

FiO_2: fractional inspired oxygen

H

HAP: hospital-acquired pneumonia

I

ICIS: intensive care information system

ICU: intensive care unit

IDSA: Infectious Diseases Society of America

INTEC: Department of Information Technology of the Faculty of Engineering of Ghent University

IQR: interquartile range

IT: information technology

IWT: Institute for the Promotion of Innovation through Science and Technology in Flanders

L

LEBA: local ecology based algorithm

LOS: length of stay

LVAD: left ventricular assist device

M

MALDI-TOF: matrix assisted laser desorption ionization time-offlight

MDR: multidrug-resistant

MICU: medical intensive care unit

MRSA: methicillin-resistant *Staphylococcus aureus*

N

NFP: non-fermenting pathogen

NHSN: National Healthcare Safety Network

P

PaO_2:	arterial oxygen tension
PBS:	paper-based surveillance
PCD:	percutaneous drainage
PCR:	polymerase chain reaction
PCT:	procalcitonin
PIDS:	Pediatric Infectious Diseases Society

R

RCT:	randomized controlled trial
RTI:	respiratory tract infection

S

SAPS:	simplified acute physiology score
SC:	surveillance culture
SCBA:	surveillance culture based algorithm
SHEA:	Society for Healthcare Epidemiology of America
SICU:	surgical intensive care unit
SIRS:	systemic inflammatory response syndrome
SOFA:	sequential organ failure assessment score
SSC:	Surviving Sepsis Campaign
SSI:	surgical site infections

U

UTI:	urinary tract infection

V

VAE:	ventilator-associated event
VAP:	ventilator-associated pneumonia
VAT:	ventilator-associated tracheobronchitis

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Birds singing a song

Old paint is peeling

This is that fresh

That fresh feeling

Words can't be that strong

My heart is reeling

This is that fresh

That fresh feeling

Eels – Fresh feeling

Back cover design by Daan De Decker: “Bacteria”